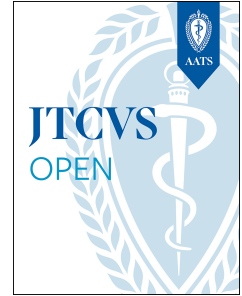


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A developmentally based proposal for neonates with hypoplastic left heart: what a great progress! But please don't stop here! A broad result is emerging

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A developmentally based proposal for neonates with hypoplastic left heart: what a great progress! But please don't stop here! A broad result is emerging.

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Central Message

A plea for the management of neonates with HLH according "medicine-based evidence". Clinical and basic scientific data support a less invasive stage-1. Waiting for "evidence-based data" is futile.

Central Picture Legend

Percutaneous S1P. Basis for mother-child bonding and beneficial outcome options.

Perspective Statement

The future acceptance of treating newborns with HLH benefits from gentle medicine that allows a more normal cognitive development. The basic requirement is a minimally-invasive transcatheter Stage-1-Procedure (S1P) enabling a normal mother-child relationship and avoidance of degenerative processes.

The great proposal by Gil Wernovsky and colleagues (1) prompted me to make some additional comments and suggestions. Perhaps pivotal was the 25th birthday of the first patient with hypoplastic left heart syndrome (HLHS) to receive a Giessen Hybrid approach in June 1998 (2), making him the world's first Hybrid survivor with a sustained good quality of life. The current proposal to treat newborns with HLHS in a less invasive way, as was intended at the time, puts the patient as a whole back at the center of medical practice.

Personalized and holistic medicine is best based on the current state of clinical and basic scientific research according to the principles of "medicine-based-evidence (MbE)" and the principle "primum nil nocere". But at the frontier of clinical medicine, one waits in vain to treat on the path of evidence-based-medicine (EbM). The pioneers Blalock-Taussig, Glenn, Fontan, Norwood and Bailey did not have EbM data. Yet, based on their pathophysiological considerations, they gave children with single ventricle physiology in general, and newborns with HLHS in particular, a chance at life. This feat has been achieved very convincingly. However, since long-term survival rate for Norwood or Hybrid procedures has plateaued at 60 to 80%, the focus of surgical and percutaneous treatments today must be *quality of life*. Given that life expectancy after completing a Fontan-circulation will remain well below the usual population average, Mozart's creative life, with a life-span of only 35 years, could serve as a model for our medical practice. The individual genetic endowment must therefore be protected. Epigenetic factors that shape endogenous regeneration should be supported and those that force cardiac and especially neurocognitive degeneration should be avoided. The authors point to two high-risk periods (1). One concerns the transitional circulation immediately after birth, the other the early postoperative period after neonatal Norwood surgery. The detrimental impact of endogenous and exogenous stress factors has been impressively described (1). Fortunately, nowadays the translation of alternative clinical and basic-science findings into clinical practice permits a far better start into life: based on the availability of catheter-based interventions, a holistic treatment concept enables parents'

existential interaction with their newborn baby with HLHS (**Figure 1**). It nurtures postnatal parental bonding and avoids interfering with the natural developmental potential through extensive cardiac operations and intensive care with hospital stays averaging two months.

The synthesis of Einstein's und Hahn's insights that "problems cannot be solved with the same mindset that created them, but with a willingness to relinquish beliefs about them" opens necessary new doors to a less invasive treatment of newborns with HLHS.

Surgical stage-1 procedure (S1P) of newborns with HLHS and variants can already be completely replaced by less invasive transcatheter techniques. The feasibility and effectiveness of percutaneous S1P has already been demonstrated (**3**). Now their standardized application with custom-made materials integrated into a comprehensive therapy protocol is required.

Currently, the percutaneous endovascular pulmonary arterial banding technique is based on approved microvascular plugs (MVP-5,7,9Q, Medtronic®). The manually created flow restrictors (PFRs) can be inserted via small diagnostic catheters and enable minimally invasive treatment of newborns and infants with life-threatening congenital and acquired heart diseases beyond S1P (**4, 5**). Many international centers have started transcatheter programs to control excessive pulmonary blood flow, balance pulmonary and systemic circulation, or improve interventricular interaction (**6**). Strategies based on tailored PFRs with and without additional duct stenting have been shown to allow delayed Norwood surgery or comprehensive stage II operation and, in neonates with hypoplastic left hearts, postponing biventricular repair attempts to later infancy (**4**). Even functional regeneration of dysfunctional and dilated left ventricles was possible by adapting PFRs to flow (**5**). In addition to cardiovascular benefits, PFR-based options also offer a reasonable chance of a better neurocognitive outcome simply by avoiding stressors, particularly for at-risk patients with HLHS and variants. Provided, however, that transcatheter implantation of bilateral PFR's is

embedded in a holistic treatment regimen.

To make PFR-based treatment successful and acceptable, its practice should not vary from center to center and the approach should only be used as rescue measure, as happened with the Hybrid approach (7). Of course, generating "best practices" of novel, patient-specific procedures require multi-center collaboration in order to generate sufficient patient numbers for drawing definitive conclusions.

Evaluable new therapies depend on coordinated and well-designed treatment plans that also include comparable patient characteristics. The latter is a dilemma shared by almost all pediatric cardiac studies labeled as "EbM". With regard to newborns with HLHS, such a study design should include a well-defined postnatal management, a consistent catheter protocol and definitively comparable materials and investigator experience. A well-defined transcatheter S1P is the prerequisite for such a minimally invasive and subsequent protective approach that supports regenerative and avoiding degenerative processes in neonatal patients. Therefore, some current "prophylactic" measures in the care of neonates with HLHS (8) should be reconsidered (**Table 1**).

Parental involvement in all aspects of care plays a crucial role in the overall development of their child. These include physical mother-child contact, oral feeding ad libitum, and teaching parents to distinguish between a healthy and a critical condition. This requires training in observing the breathing rate and drinking behavior of their infant.

In newborns with HLHS, well-intended overtreatment, such as possible overdose with continuous prostaglandin infusion, done solely on fear of ductal obstruction, should be avoided. This includes also the decision to intubate and ventilate HLHS children with arterial oxygen saturation (SaO₂) perhaps greater than 90% and to aim for values equivalent to a pulmonary/systemic flow-ratio of 1. A vicious cycle due to anesthetics and eventually muscle relaxants can inevitably be set in motion, cumulating in an infusion of catecholamines and "heart failure therapy" with diuretics.

A similar situation can occur when general anesthesia is used for transcatheter S1P instead of balanced, light analgesic sedation in a spontaneously breathing baby. Not everything is done taking into account the fragile pathophysiology, but only out of a personal sense of security. Newborns with duct-dependent systemic blood flow are at highest risks. Intubation and extubation, introduction and removal of anesthetics, and controlled ventilation with likely deleterious effects on systemic blood flow due to decreased pulmonary vascular resistance are the most obvious adverse scenarios.

In addition, it is now generally accepted that anesthetics, catecholamines, non-indicated diuretics, or other procedures that impair the regenerative capacity of the heart and/or brain should be avoided whenever possible, particularly during the neonatal period. Postnatal catecholamine serum levels of epinephrine and norepinephrine are already 10 to 20 times the normal serum levels, therefore any exogenous catecholamine treatment, except for acute resuscitation should and can be avoided. Inodilators (milrinone, levosimendan) are the drugs of choice when a failing neonatal myocardium is in real need of support. If catecholamines, especially norepinephrine, are nevertheless administered to maintain sufficient coronary perfusion pressure, this should preferably be done with simultaneous β 1-receptor blockade with a highly specific β 1-blocker such as landiolol for infusion (9) or oral bisoprolol (10). Beta1-selective beta-blockers improve hemodynamics by optimizing heart rate, diastolic filling and coronary perfusion time, systemic blood pressure amplitude with additional optimization of the Qp/Qs ratio and this with almost no side-effects, especially without bronchoconstriction due to β 2-adrenergic receptor blocking. The effectiveness of the β 1-receptor blocker is easily monitored by the decrease in heart rate and the increase in systemic blood pressure (amplitude). With the heart rate controlled, the efficiency of the bilateral PFRs as part of the transcatheter S1P, similar to the Hybrid approach, can be verified by a systolic-diastolic Doppler pattern.

Basic research and clinical data suggest that a β 1-blocker does more than just block β 1-receptors with antiarrhythmic properties (11). Beta1-adrenoreceptor blockade has been shown to prevent myocardial apoptosis and necrosis, restore ischemia-induced down-regulated excitation-contracting proteins and mitochondrial function, and further stimulate cardiac progenitor cell survival and proliferation. Cardioprotective cross-signals through residual β 2- and β 3-related mechanisms are still to be expected (11). Taking into account clinical experience with heart rate reduction and body weight gain (10), basic scientific data emphasize not only cardiac as well as neurocognitive protective aspects (12). The use of β 1-receptor blockers in patients with HLHS in general and during the interstage in particular, is overdue.

In conclusion, the pediatric cardiac community should ensure the benefits of comprehensive and disease-modifying therapy for neonates with a hypoplastic left ventricle based on percutaneous S1P. As part of a standardized and holistic therapy, the transcatheter approach could have the potential to be a real game changer. The goal of rethinking should not just focus on technical improvements that make full percutaneous S1P routine. The interventional / surgical follow-up measures including their periprocedural treatments should be considered as a whole. According to Aristotele "the whole is more than the sum of its parts". Ultimately, all measures are subordinate to the goal of enabling a newborn with HLHS to have a high quality of life.

With regard to opinion leadership, only pediatric heart surgeons can initiate such a comprehensive change in the therapeutic strategy (**Fig.1**) according to the principle "I will create something new or allow what is necessary."

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Table 1**HLHS care, measures to avoid:**

- Disturbance of mother-child interaction (parental unacceptance)
- Non-oral feeding or abstinence from feeding *ad libido* (unnecessary stress-factor)
- High-dose prostaglandin infusion (apnea, Qp:Qs imbalance)
- Intubation and ventilation to achieve a Qp/Qs ratio of 1 (inadequate in term of risk-benefit ratio)
- General anesthesia or use of anesthetic drugs (inadequate for transcatheter S1P)
- Application of catecholamines (β 1-related apoptosis, degenerative; HR +, MVO₂ increase)
- Routine use of diuretics (neurohumoral activation, intravascular volume depletion, R_s increase)
- None routine administration of β 1-selective blockers (hemodynamic and regenerative support)

Legend Figure 1**Proposal for transcatheter stage-1 treatment in a standard-risk newborn with HLHS**

Adapted to Figure 1; Gil Wernovsky et al. (1).

Abbreviations: ASS, acetyl salicylic acid; ECHO, echocardiography; LPA, left pulmonary artery; PA, pulmonary artery; PFR, pulmonary flow restrictor; PGE, prostaglandin; RPA, right pulmonary artery; S1P, stage 1 procedure; S2P, stage 2 procedure;

