Progress in Pediatric Cardiology 54 (2019) 101132

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Review

The 19th annual C. Walton Lillehei memorial lecture in cardiovascular surgery customizing single ventricle care

Jonathan M. Chen*

Division of Cardiothoracic Surgery Mortimer J. Buckley, Jr. Endowed Chair Co-Executive Director, Cardiac Center Children's Hospital of Philadelphia 3401 Civic Center Boulevard Philadelphia, PA 19104

C. Walton Lillehei requires no introduction to congenital cardiac audiences around the world. He is widely considered the father of modern cardiac surgery, an innovator, and an unparalleled and fearless thought leader. Almost as important as the advances Lillehei's work contributed to the field of cardiopulmonary bypass, there are many lessons to be learned from his observations on the challenges of implementing surgical innovation. In an address he gave in 1984, Lillehei outlined the so-called "7 ages in the evolution of an idea" in which he documented the response by critics to the introduction of novel therapies (Table 1) [1]. These Kubler-Ross type stages follow the philosophical resistance to new paradigms from basic cynicism, to disruptive gossip, to smug self-revisionist history. As we look toward the future of our field, whether under the guise of public reporting, or in the face of other academic scrutiny, the resistance to novel therapies is pervasive.

Some would argue that despite the major advances that have contributed to our understanding of single ventricle physiology, our surgical management has remained largely the unchanged since its early inception. In fact, almost 20 years before the Fontan principle was described, Rodbard and Wagner suggested that one might bypass the right ventricle and allow venous pressure to drive pulmonary blood flow [2]. Nearly a decade later, Nuland and colleagues took this one step further to contemplate clinical conditions for which this surgical therapy could be applied (Table 2) [3]. Interestingly, most notably in Nuland's description of this canine model of systemic venous to pulmonary artery connection, he also described significant pleural effusions and chylous drainage in those animals surviving beyond one month, perhaps presaging the exciting renaissance in lymphatic focus we are now enjoying today (Fig. 1).

The iconic description in 1971 by Fontan and Baudet of three patients undergoing a new approach to 'repair' of tricuspid atresia ushered in a new era for congenital heart surgery in the realm of single ventricle palliation [4]. Fast forward to today, in which the Fontan procedure represents a common pathway destination in the management of a dizzyingly heterogeneous array of anatomic subtypes– all of which share in common the need for a single common systemic pumping chamber—from 'garden variety' hypoplastic left heart syndrome to complex heterotaxy variants. While the Fontan procedure itself has undergone a series of modifications over the past fifty years, the most popular today may be distilled down to the lateral tunnel and extracardiac conduit.

We envision this pathway toward the common end (Fontan) as being relatively reproducible and predictable. In the ideal scenario, a child is born with a fetal diagnosis of single ventricle disease, may or may not undergo 1st stage palliation, is discharged home and returns for 2nd stage palliation, is again discharged and returns for Fontan completion. However, somewhat frequently this idealized pathway is often fraught with complications—perinatal crises, the need for interstage invasive procedures, prolonged hospitalizations—all of which conspire to impact on the relative success of Fontan completion. Indeed, the results of the Fontan are far from predictable, and our ability to anticipate which patients will go on to develop mucosal derangements (protein losing enteropathy, plastic bronchitis), cardiomyopathy requiring transplant, or circuit failure is regrettably quite inexact. Because of this, one of the most fundamental fallacies of our current approach to single ventricle care is that one size does not, in fact, fit all; no two single patients and no two single ventricle variants are exactly alike.

Many ask what will be the next breakthrough surgical innovation or operation for single ventricle patients with an impact of the magnitude of a Norwood procedure or Fontan operation. As our understanding of the complexity of congenital heart disease grows, it may in fact be that the paradigm shift will have to be away from the dream of a single 'disruptive' correction toward the development of collaborative 'disruptive' *strategies* of congenital heart care that are implemented from conception to adulthood and may be *tailored* to the individual.

Indeed, the Norwood procedure has not changed substantively since its first description in 1983, in which the concept of the amalgamation of the great vessels, arch reconstruction, atrial septectomy and provision of restricted pulmonary blood flow remains foundational [5]. The review by Mascio et al. of more than 1600 Norwood patients across several decades of care at the Children's Hospital of Philadelphia interestingly demonstrated improvement over the early eras of care, but also a lower mortality threshold that has persisted since the year 2000 [6]. As important, in further evaluating the drivers of the mortality

* Corresponding author.
E-mail address: chenj14@email.chop.edu.

https://doi.org/10.1016/j.ppedcard.2019.101132
Received 18 May 2019; Received in revised form 14 July 2019; Accepted 29 July 2019
Available online 01 August 2019
1058-9813/

Table 1
Lillehei's seven ages in the evolution of an idea [1].

I. Idea stage	"Won't work"
	"Been tried before"
II. Successful experiments (in animals)	"Won't work in man"
III. After one successful clinical patient	"Very lucky"
	"Doubt if patient really needed treatment"
IV. After 4–5 clinical successes	"Too bad, a tragedy really because now they'll continue"
V. After 10–15 patients	"Experimental, unethical"
	"I understand they had a number of deaths they're NOT reporting"
VI. After a large series	"May succeed occasionally in carefully selected cases…"
	"I hear that a number of their patients are now dying late deaths"
VII. Final stage	"I predicted this. In fact, in 1929 I had the same idea"

Table 2
Nuland's "conditions that might benefit from right heart bypass" [3].

A. Involving heart:
  a. Tricuspid atresia
  b. Hypoplasia of right ventricle
  c. Ebstein's anomaly
B. Involving pulmonary artery
  a. Pulmonic stenosis with or without
    i. Single ventricle
    ii. Bilocular heart
    iii. Transposition of the great vessels
C. Involving vena cava
  a. Anomalous insertion into left atrium
  b. Obstruction, congenital or acquired

limit, he demonstrated the profound additive effect of patient risk factors that themselves likely surpass any iterative intraoperative improvements that could be implemented; in this series those with four or more risk factors (Table 3) demonstrated a sobering 40% operative mortality. Notably, of these patient risk factors listed, most are not modifiable.

Gaynor and colleagues in parallel have focused much of their work characterizing the effect of the maternal-fetal environment on surgical outcomes [7]. In their study, the acquisition of *one* of four risk factors (gestational hypertension, pre-eclampsia, small for gestational age or preterm birth) conferred a profound impact on operative mortality. This acknowledgment has encouraged investigators to more aggressively investigate the potential for the so-called 'artificial womb' that might allow for mitigation of these otherwise unmodifiable factors and in essence change the cards before they are dealt [8].

Lawrence and colleagues used this animal model to simulate conditions of hypoxia not unlike those present for fetuses with congenital heart disease [9]. In their proof-of-concept model, they importantly demonstrated abnormal myocardial development in the setting of a hypoxemic fetal environment. With this in mind, the logical next question is whether altering this hostile hypoxic environment can change the deleterious effects of in utero hypoxia, and thereby potentially reduce later newborn operative risk.

Without question there are surgical advances in technique that can leverage evolving imaging technology to guide intraoperative reconstruction. Three dimensional imaging has been used to suggest a relationship between similarity to idealized aortic arch reconstruction in the Norwood and late outcomes, and in some centers these models have directed surgical arch reintervention at the second stage procedure solely based on numerical flow analysis [10]. Moreover, the one-size-fits-all is no more resonant than in the case of the extra cardiac conduit, in which premade PTFE tube grafts are used off the shelf for nearly all anatomic variants of single ventricle physiology. The dream of a customized, potentially bifurcated, conduit has been realized as proof of concept by Yoganathan and colleagues at Emory [11]. Yet the true dream of a customized printed conduit—one that takes into account optimized balanced flow, mixing and flow dynamics—is a bespoke creation that may not be so far in the future for implantation [12].

Refinements in our understanding of the anatomical substrate that presages later disease complications ultimately may push us to consider *preemptive* interventions. Jolley and coworkers have focused their work on the tricuspid valve of newborns with HLHS in an effort to better characterize and profile the morphology of those valves that go on to develop early insufficiency and help develop patient specific valve repair strategies that could be considered (even prophylactically) at stage 2 palliation [13]. Our evolving understanding of the importance of lymphatic architecture on the potential for later development of debilitating chylous effusions or other mucosal derangements after Fontan completion has further provided an important platform to consider preemptive procedures (e.g., lymphovenous anastomoses, innominate vein turn down) to perform pre-Fontan so as to mitigate or eliminate their later development [14].

Single ventricle disease provides a very unforgiving physiology. While the ultimate goal of cavo-pulmonary connection remains the same, the means by which patients arrive there—and more important the success and health of the final palliated state—is variable. Our job as we look toward the future of congenital cardiac care is to devise customized strategies of care that involve the fewest detours, and maximize the likelihood that our patients might lead their healthiest lives thereafter. We need to move from a notion of "one size fits all" toward one of customized strategies of care that will help to personalize this journey for our individual patients.

Recall again the idealized pathway that leads ultimately to staged palliation of single ventricle disease and consider two hypothetical patients with HLHS. The first is one in whom a prenatal genetic profile predicts a profile unfavorable for postnatal survival. Imagine that this baby is unfortunately born prematurely and so is placed in the artificial womb for 7 weeks under hyperoxic conditions, delivered, and because of this history undergoes bilateral pulmonary artery banding and staged Norwood procedure 4 weeks later. The baby is evaluated pre-Glenn and found to have the anatomic profile presaging ongoing lymphatic derangements and the development of atrioventricular valve regurgitation and so undergoes a preemptive innominate vein turn down and tricuspid valve repair. At a slightly later age of 5 years of age, three dimensional imaging allows for the creation of a custom conduit, which is implanted and maximizes the likelihood of an excellent quality of life.

The other patient is one whose genetic profile is normal, but is found to have an nearly intact atrial septum on fetal imaging. This child undergoes a fetal intervention to enlarge the septum and because of the this fetal course, the baby undergoes a hybrid procedure, a comprehensive stage two operation, and because the MRI at 3 years of age suggests stage IV lymphatic disease and liver elastography predicts early cirrhosis, the child proceeds straight to heart transplantation early (despite seemingly normal ventricular function), so as to reduce the likelihood of requiring dual organ transplantation, and obviating the pathway that would produce Fontan failure pre-transplant (Fig. 2). For this child, this particular flight plan will yield the highest likelihood of long term success.

Complex congenital care is a game of chess played across several

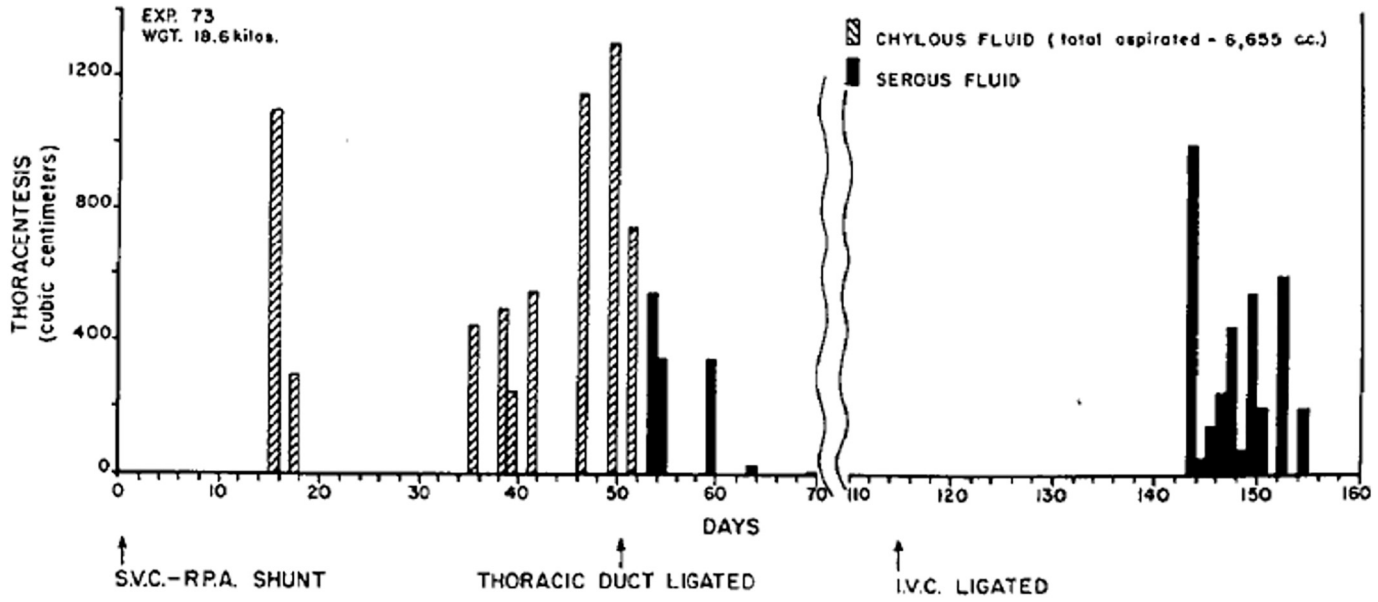

Fig. 1. Pleural effusions following superior vena cava-right pulmonary artery shunt [3].

Table 3
Patient factors contributing to operative mortality after Norwood procedure [6].

Anomalous pulmonary venous return
Moderate/severe atrioventricular valve regurgitation
Preterm birth (< 37 weeks)
Presence/suspicion of genetic anomaly
Intact/highly restrictive atrial septum
Preoperative intubation
Weight at surgery

domains of time and space—one that seeks to allow our patients to lead their healthiest lives with the fewest number of interventions and hospitalizations along the way. One of our challenges for certain will be to embrace not only the notion of being proactive, but more important to have the courage to undertake certain strategies of care and interventions that are preemptive and preventative (but potentially unproven), despite the criticisms across Lilleihei's seven ages of a new idea.

To succeed at this requires an expert collaborative cardiac center that fires on all cylinders. (Fig. 3) Each of us within our own domains has a profound responsibility to implement relentless iterative

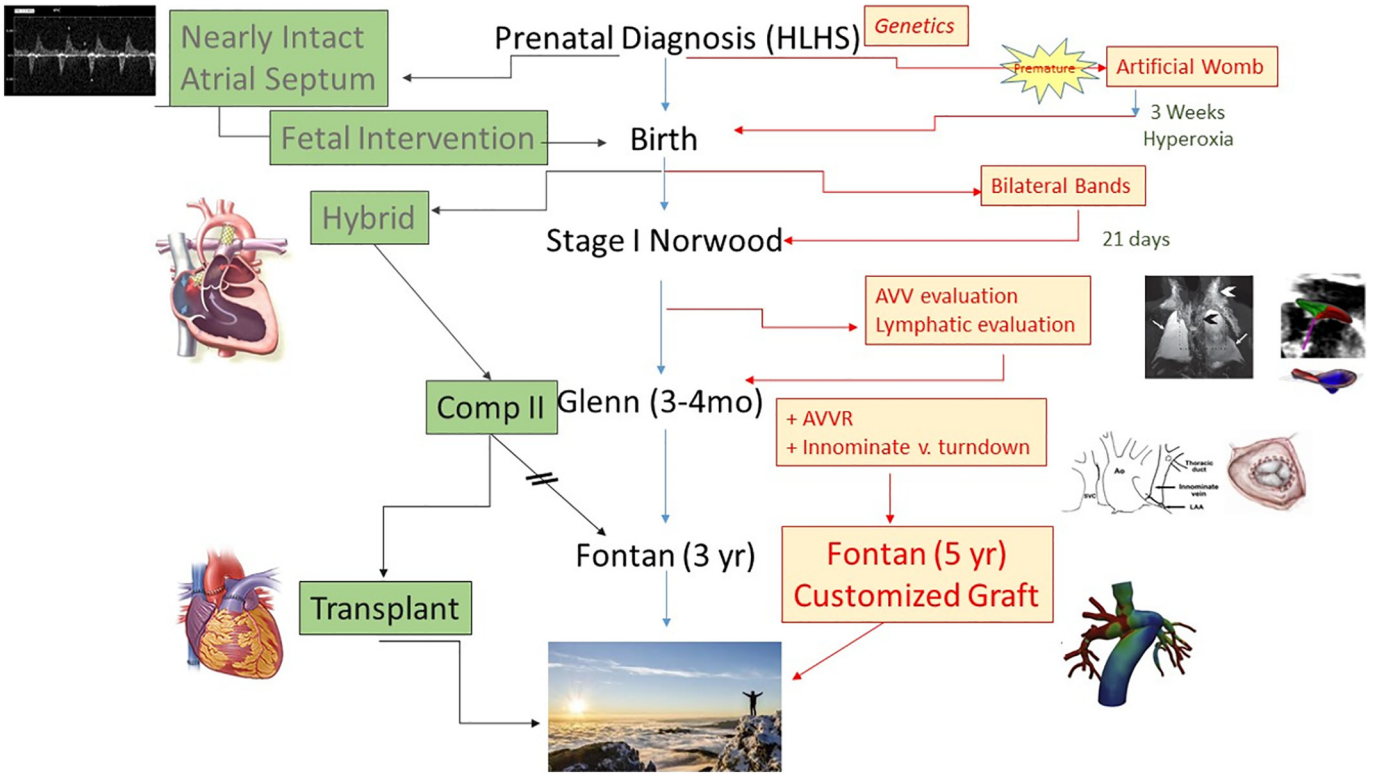

Fig. 2. Two potential customized pathways for two hypothetical patients.

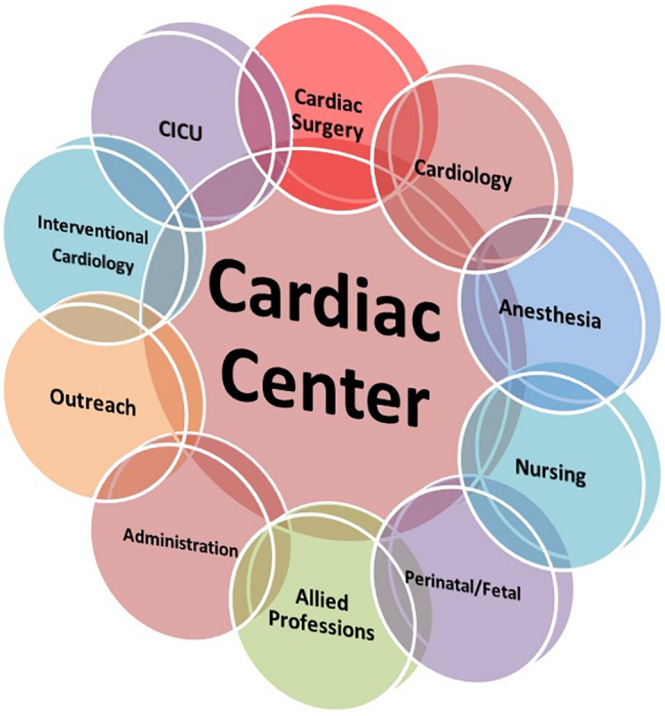

Fig. 3. The ideal Cardiac Center structure.

improvement in the care of single ventricle patients, that they might be able to call their care strategy theirs and theirs alone.

An apocryphal tale of Walt Lillehei posits that Owen Wangentstein had demonstrated success with development of an external pacemaker device on dogs in the laboratory, and that Lillehei, so enamored of the invention, stole it from the laboratory and used it for one of his patients in the intensive care unit thereby saving his life and ushering in a new era of artificial pacemaker technology. The days of such bold (and potentially reckless) clinical application of innovation are perhaps appropriately over. However, we need to harness that spirit of risk taking despite seven phases of critique that greet us; we need to take on the daunting challenge of customizing congenital cardiac care.

Declaration of competing interest

I serve as a consultant to the Medtronic and Gore corporations for two independent clinical trials.

References

[1] Lillehei CW. A personalized history of extracorporeal circulation. Amer Soc Artif Intern Org 1982;28:4–17.
[2] Rodbard S, Wagner D. Bypassing the right ventricle. Proc Soc Exp Biol Med 1949;71(1):69–70.
[3] Nuland SB, Glenn WL, Guilfoil PH. Circulatory bypass of the right heart. Surgery 1958;43(2):184–201.
[4] Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26(3):240–8.
[5] Norwood WI, Lang P, Hansen DD. Physiologic repair of aortic atresia-hypoplastic left heart syndrome. N Engl J Med 1983;308(1):23–6.
[6] Mascio CE, Irons ML, Ittenbach RF, Gaynor JW, Fuller SM, KAplinski M, Kennedy AT, Steven JM, Nicolson SC, Spray TL. Thirty years and 1663 consecutive Norwood procedures: has survival plateaued? J Thorac Cardiovasc Surg 2019;159(1):220–9.
[7] Gaynor JW, Parry S, Moldenhauer JS, Simmons RA, Rychik J, Ittenbach RF, et al. The impact of maternal-foetal environment on outcomes of surgery for congenital heart disease in neonates. Eur J Cardiothorac Surg 2018:348–53.
[8] Partridge EA, Davey MG, Hornick MA, Flake AW. An EXTrauterine environment for neonatal development: EXTENDING fetal physiology beyond the womb. Semin Fetal Neonatal Med 2017;22(6):404–9.
[9] Lawrence KM, Hennessy-Strahs S, McGovern PE, Mejaddam AY, Rossidis AC, Baumgarten HD, et al. Fetal hypoxemia causes abnormal myocardial development in a preterm ex utero fetal ovine model. JCI Insight 2018 Dec 20;3(24).
[10] Myazaki S, Miyaji K, Itatani K, Oka N, Goto S, Nakamura M, et al. Surgical strategy for aortic arch reconstruction after the Norwood procedure based on numerical flow analysis. Interact Cardiovasc Thorac Surg 2018;26:460–7.
[11] Trusty PM, Restrepo M, Kanter KR, Yoganathan AP, Fogel MA, Slesnick TC. A pulsatile hemodynamic evaluation of the commercially available bifurcated Y-graft Fontan modification and comparison with the lateral tunnel and extracardiac conduits. J Thorac Cardiovasc Surg 2016;151:1529–36.
[12] Trusty PM, Slesnick TC, Wei ZA, Rosslgnac J, Kanter KR, Fogel MA, et al. Fontan surgical planning: previous accomplishments, current challenges, future directions. J Cardiovasc Transl Res 2018;11:133–44.
[13] Pouch AM, Aly AH, Lasso A, Nguyen AV, Scanlan AB, McGowan FX, et al. Image segmentation and modeling of the pediatric tricuspid valve in hypoplastic left heart syndrome. Funct Imaging Model Heart 2017;10263:95–105.
[14] Dori Y. Novel lymphatic imaging techniques. Tech Vasc Interv Radiol 2016;19(4):255–61.