Survival Outcomes after Fontan

It is not a "Repair"

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Professor of Medicine and Pediatrics
Mayo Clinic
CHOP/IFIG Meeting, February 2018

No Disclosures

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Saji Oommen
Susana Cantero Peral

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What we will cover this morning …

- History of the Fontan operation
- Issues after Fontan operation
- Outcomes after Fontan operation
- Future for patients after Fontan

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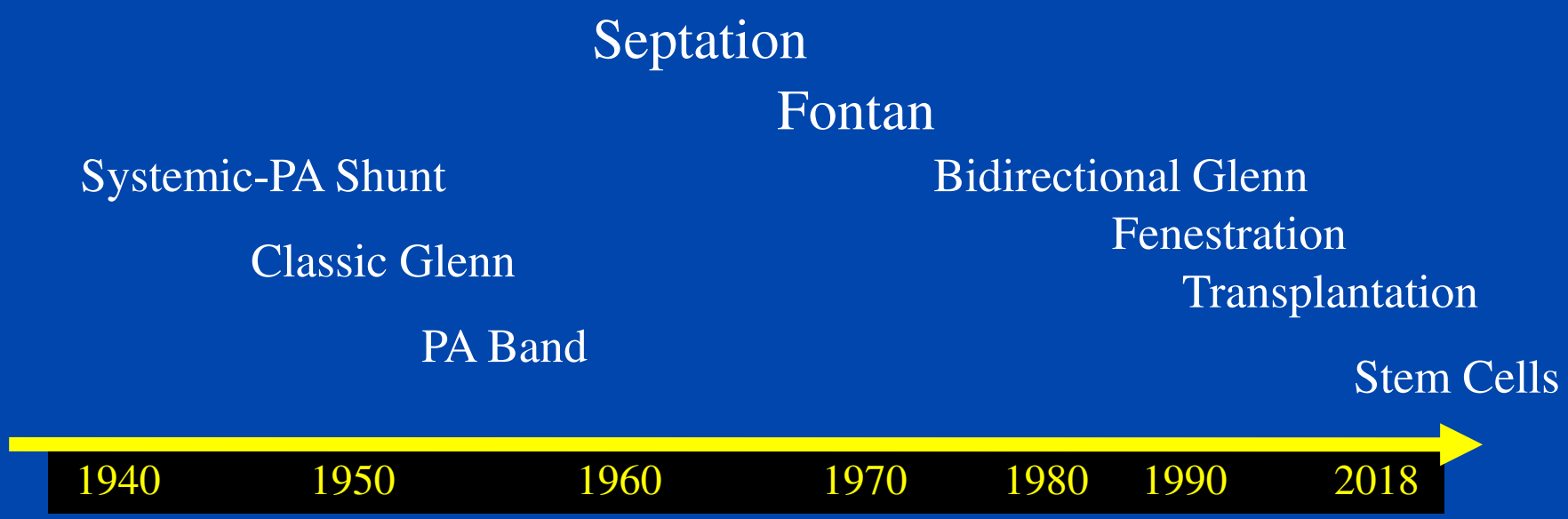
Evolution of Management for Patients with Single Ventricle Physiology



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Evolution of Thinking

- 1970s → 1990s:
  - "*Get all patients with functional single ventricle to Fontan*"
- Currently:
  - "*The worst thing we do is create a BAD Fontan*"

The Fontan Palliation

1929 - 2018

Thorax (1971), **26**, 240.

Surgical repair of tricuspid atresia

F. FONTAN and E. BAUDET

Centre de Cardiologie, Université de Bordeaux II, Hôpital du Tondu, Bordeaux, France

Surgical repair of tricuspid atresia has been carried out in three patients ; two of these operations have been successful. A new surgical procedure has been used which transmits the whole vena caval blood to the lungs, while only oxygenated blood returns to the left heart. The right atrium is, in this way, 'ventriclized', to direct the inferior vena caval blood to the left lung, the right pulmonary artery receiving the superior vena caval blood through a cava-pulmonary anastomosis. This technique depends on the size of the pulmonary arteries, which must be large enough and at sufficiently low pressure to allow a cava-pulmonary anastomosis. The indications for this procedure apply only to children sufficiently well developed. Younger children or those whose pulmonary arteries are too small should be treated by palliative surgical procedures.

Only palliative operations (systemic vein to pulmonary artery anastomosis ; systemic artery to pulmonary artery anastomosis) have been performed in tricuspid atresia. Although these procedures are valuable, they result in only a partial clinical improvement, because they do not suppress the mixture of venous and oxygenated blood.

We have initiated a corrective procedure for tricuspid atresia, which completely suppresses blood mixing. The entire vena caval return undergoes arterialization in the lungs and only oxygenated blood comes back to the left heart. This procedure is not an anatomical correction, which would require the creation of a right ventricle, but a procedure of physiological pulmonary blood flow restoration, with suppression of right and

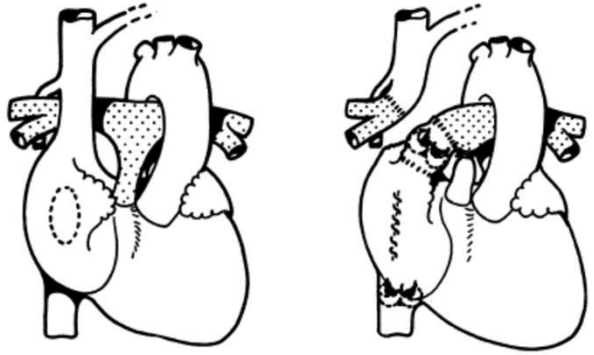

FIG. 1. *Case 2. Tricuspid atresia type II B. Drawing illustrates steps in surgical repair:* (1) *end-to-side anastomosis of distal end of right pulmonary artery to superior vena cava;* (2) *end-to-end anastomosis of right atrial appendage to proximal end of right pulmonary artery by means of an aortic valve homograft;* (3) *closure of atrial septal defect;* (4) *insertion of a pulmonary valve homograft into inferior vena cava; and* (5) *ligation of main pulmonary artery.*

Fontan Operation: The Reasons

- Eliminate cyanosis
  - Reduce risk of stroke
- Eliminate volume overload
  - Preserve ventricular function
- Improve exercise tolerance
- Prolong life

Fontan's Advice

"These (Fontan) operations are *not curative*…they should not always be indicated if another less risky option is available…wrong indications…are responsible for early takedowns. Poor late results…which are the shame of this operation, should disappear if we attach the greatest importance to not transgressing absolute contraindications"

Fontan F. JTCVS, 1986: 92:1045

TABLE 38.2 Choussat and Fontan Original Operative Criteria

1. Age at operation between 4 and 15 yrs
2. Presence of sinus rhythm
3. Normal systemic venous return
4. Normal right atrial volume
5. Mean pulmonary artery pressure <15 mm Hg
6. Pulmonary arteriolar resistance <4 $u m^2$
7. Ratio of pulmonary artery diameter to aorta diameter >0.75
8. Left ventricular ejection fraction >60%
9. Competent mitral valve
10. No adverse effect from prior pulmonary artery operation

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The Fontan Palliation

- "Surgically created "un-*physiology*"
- Caval blood → lungs
  - without a ventricular pump
- Many "modifications"
- Not a "repair", "correction", or "cure"

Parameters Related to a Successful Fontan

- Normal systolic & diastolic performance
  - Low filling pressure, high compliance
- Low PA pressure & resistance
  - PA size matters … small is bad
- Only mild AV valve regurgitation
- No obstruction:
  - Fontan, PAs, PV, outflow tract, aorta
- Sinus rhythm

Spectrum of Fontan Connections

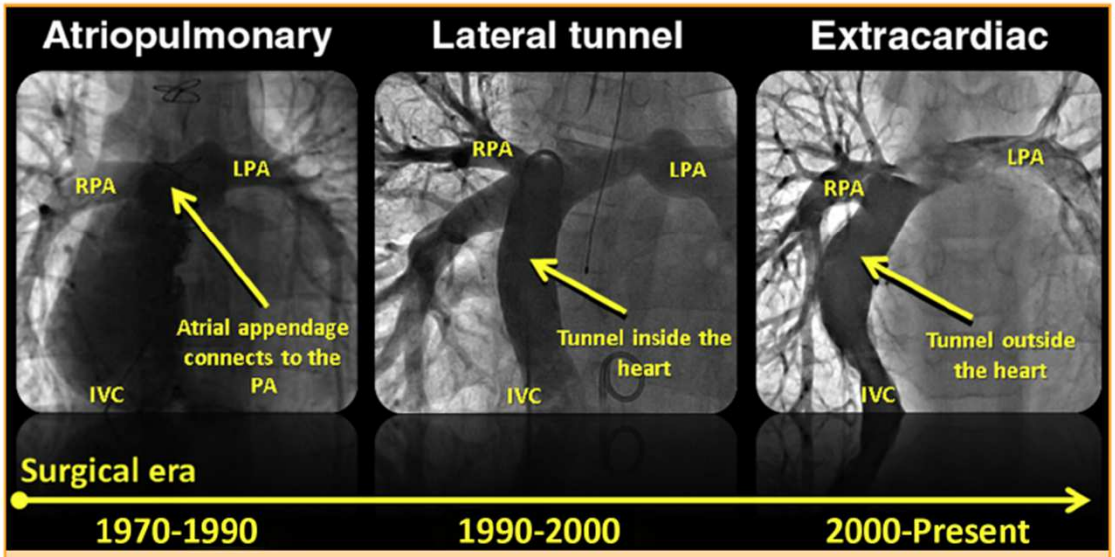

FIGURE 1. Fontan surgical subtypes. The Fontan operation consists of rerouting systemic bicaval venous return directly into the pulmonary arterial confluence, effectively bypassing the subpulmonary ventricle. These angiograms demonstrate the Fontan subtypes in order of the surgical era: atriopulmonary, in which the right atrial appendage is directly sewn to the pulmonary arterial confluence, the superior vena cava is left in continuity with the atrium, and the atrium acts as a functional conduit (left); lateral tunnel, in which the conduit lies within the right atrium, connecting the inferior vena cava (IVC) to the pulmonary artery (PA) and the superior vena cava is sewn directly to the right PA (middle); and the extracardiac type of Fontan connection, in which a conduit lying outside the heart connects the IVC to the inferior portion of the pulmonary arterial confluence and the superior vena cava is sewn directly to the right PA (right).

The modern Fontan operation shows no increase in mortality out to 20 years: A new paradigm

Robert J. Dabal, MD,[a] James K. Kirklin, MD,[a] Manisha Kukreja, MBBS, MPH,[a] Robert N. Brown, BS,[a] David C. Cleveland, MD,[a] Michael C. Eddins, MD,[b] and Yung Lau, MD[c]

Objective: Dating back to the first published report of the Fontan circulation in 1971, multiple studies have examined the long-term results of this standard procedure for palliation of single-ventricle heart disease in children. Although the technique has evolved over the last 4 decades to include a polytetrafluorethylene (PTFE) conduit for a large percentage of patients, the long-term outcome has not yet been established. The aim of the current study was to investigate the possibility of a late increasing risk for death after 15 years among patients with a modern Fontan operation and to evaluate late morbidity.

Methods: Between January 1, 1988, and December 31, 2011, 207 patients underwent the Fontan procedure using an internal or external PTFE conduit plus a bidirectional cavopulmonary connection. Survival and late adverse events were analyzed. Risk factors for early and late mortality were examined using hazard function methodology.

Results: At 1, 10, and 20 years, survival for the entire cohort was 95%, 88%, and 76%, respectively, with no deaths in the last 6 years of the study. Hazard modeling showed a 1.3% risk of death per year 24 years after the Fontan procedure, with no late increasing hazard phase. Freedom from reoperations was greater than 90% at 20 years and freedom from thrombotic complications was 98% at 20 years (with greater than 80% of patients on aspirin alone). Survival curves were superimposable for 16- to 20-mm conduits, and the freedom from any reoperation including transplantation was greater than 90% after 20 years. Multivariable risk factor analysis identified only earlier date of operation as a predictor of early and late mortality. By era of surgery, the 10-year predicated survival is 89% for patients undergoing surgery in 2000 and 94% for patients in 2010.

Conclusions: Early and late survival after a Fontan operation with a PTFE conduit is excellent, with no late phase of increasing death risk after 20 years. Late functional status is good, the need for late reoperation is rare, and thrombotic complications are uncommon on a standard medical regimen including aspirin as the only anticoagulation medication. (J Thorac Cardiovasc Surg 2014;148:2517-24)

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Which size ECC is best?
16 mm or larger?

Issues after Fontan

- Arrhythmia
- Heart Failure
- Cyanosis
- PLE
- Thrombosis
- Plastic Bronchitis
- Hepatic Dysfunction
- Pregnancy ?

Issues after Fontan

- **Arrhythmia**
  - > 60%, IART, Afib/flutter
- **Heart Failure**
  - PHN study: 27% systolic; 72% diastolic
- **Cyanosis**
  - Veno-veno collaterals, pul. AV fistula
- **PLE – 10%**
  - ↑ mesenteric vascular resistance
  - inflammation

Issues after Fontan

- **Thrombosis**
  - 5-7% baffle, RA, PA, PA stump
  - antiplatelet vs. warfarin Rx
- **Plastic Bronchitis**
  - 1-2% - cast formation, difficult to Rx
- **Hepatic Dysfunction**
  - chronic elevation of CVP
  - fibrosis, cirrhosis, nodularity, HCC
  - Increased frequency, Rx ?
  - Heart/liver Tx ?

FALD
Fontan Associated Liver Disease
Fontan Physiology Compromises other Organs

- Hypoxemia with low cardiac output
- Chronic ↑ CVP
- Chronic ↑ mesenteric vascular resistance

- Plus: perioperative insults, atrial arrhythmias, HCV infection

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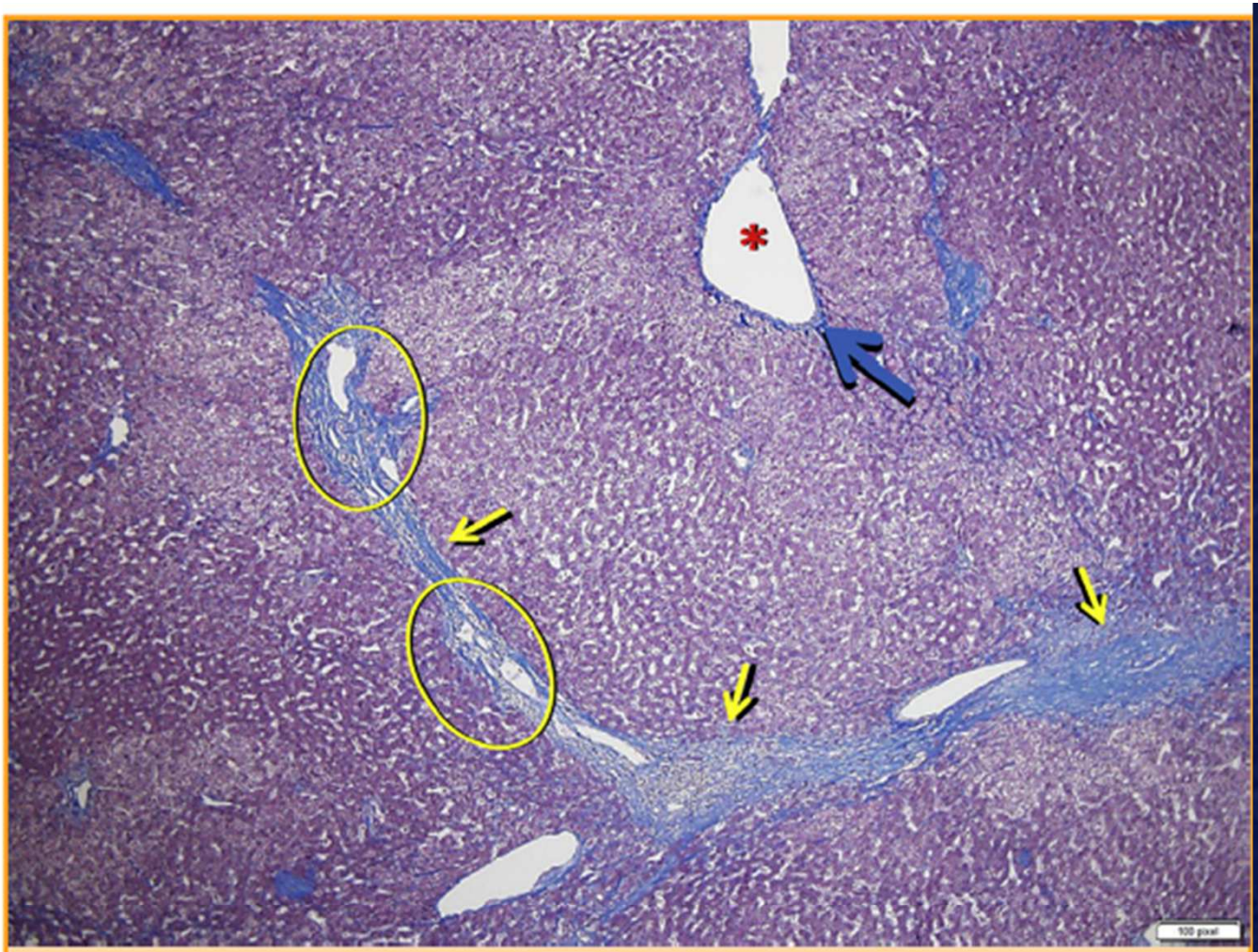

FIGURE 7. Typical histologic findings of Fontan-related cirrhosis. The figure (Masson trichrome stain, magnification 40×) shows bridging portal fibrosis (portal triads circled in yellow, bridging fibrosis depicted by yellow arrows, and central vein depicted by the red asterisk) and centrilobular and perisinusoidal fibrosis (blue arrow). Sinusoidal hepatic cells are vulnerable to ischemic injury in low cardiac output as in the Fontan physiology.

REVIEW ARTICLE

WILEY Congenital Heart Disease

Surveillance for liver complications after the Fontan procedure

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Abstract

The physiological consequences of the Fontan circulation impose risk for hepatic dysfunction and may culminate in hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. Consensus regarding appropriate surveillance modalities to diagnose liver disease in Fontan patients is lacking, in part due to the relative lack of strong evidence and prospective studies in this patient population. The goal of this paper is to critically review the current evidence and provide recommendations for the surveillance of hepatic complications in the post-Fontan patient population.

KEYWORDS
cirrhosis, Fontan

1 | INTRODUCTION

The Fontan procedure is considered the definitive palliation for patients with single-ventricle physiology.[1] The procedure, which has had many modifications over the decades, results in an anastomosis between the vena cavae or right atrium and the pulmonary arteries, whereby systemic venous blood is returned to the lungs without utilizing a pumping chamber.[1,2] The Fontan operation maintains near-normal systemic oxygenation while inducing a state of systemic venous hypertension and relatively decreased cardiac output.[2] The physiological consequences of the operation place individuals with a Fontan circulation at risk for long-term complications related to passive venous congestion of the liver.[3,4] A recent long-term follow-up study reported 10-, 20-, and 30-year survival of 74%, 61%, and 43% respectively after the Fontan procedure.[5] As more patients reach adulthood,[6,7] hepatic complications are increasingly recognized.[8] Therefore, implementation of evidence-based surveillance and management of post-Fontan hepatic complications is essential in this population. The goal of this paper is to synthesize the relevant literature and define an approach to the surveillance of hepatic complications in the post-Fontan patient population.

2 | PATHOPHYSIOLOGY OF LIVER DYSFUNCTION IN FONTAN PATIENTS

Hepatic dysfunction after the Fontan operation is multifactorial and may culminate in hepatic fibrosis and cirrhosis.[9] Recent reports of hepatocellular carcinoma in patients after Fontan operation have added further concern.[10] The hepatic changes secondary to the Fontan circulation may be divided broadly into those related to passive venous congestion; low cardiac output; and complications of portal hypertension. It should be recognized that in many patients, passive venous congestion and low cardiac output coexist.

Several of the physiologic derangements inherent to the Fontan circulation compromise the liver, including hypoxemia in the setting of chronic low cardiac output state, chronic elevation of central venous pressure, and increased mesenteric vascular resistance. It is important to note that while not all Fontan patients have low cardiac output, studies suggest that cardiac output is on average decreased in Fontan patients.[11,12] A retrospective review of catheterization data from adult and pediatric Fontan patients reported average cardiac indices of 2.7 ± 0.8 and 2.8 ± 0.7 L/min/m^2, respectively (normal range 2.5–4.0 L/min/m^2).[12] Patients may have also perioperative ischemic insults to the liver, or veno-venous connections which compound hypoxic injury to the liver.[14] Over time, "Fontan failure" may develop with further elevations in systemic venous pressure, decline in cardiac output, and multisystem dysfunction. Protein-losing enteropathy (PLE) develops in 10–15% of patients.[15] Continuous systemic venous back-pressure on the liver results in hepatic changes secondary to passive venous congestion. This passive venous congestion is continuous, in contrast to the more intermittent or pulsatile back-pressure experienced in congestive hepatopathy associated with other cardiac defects,

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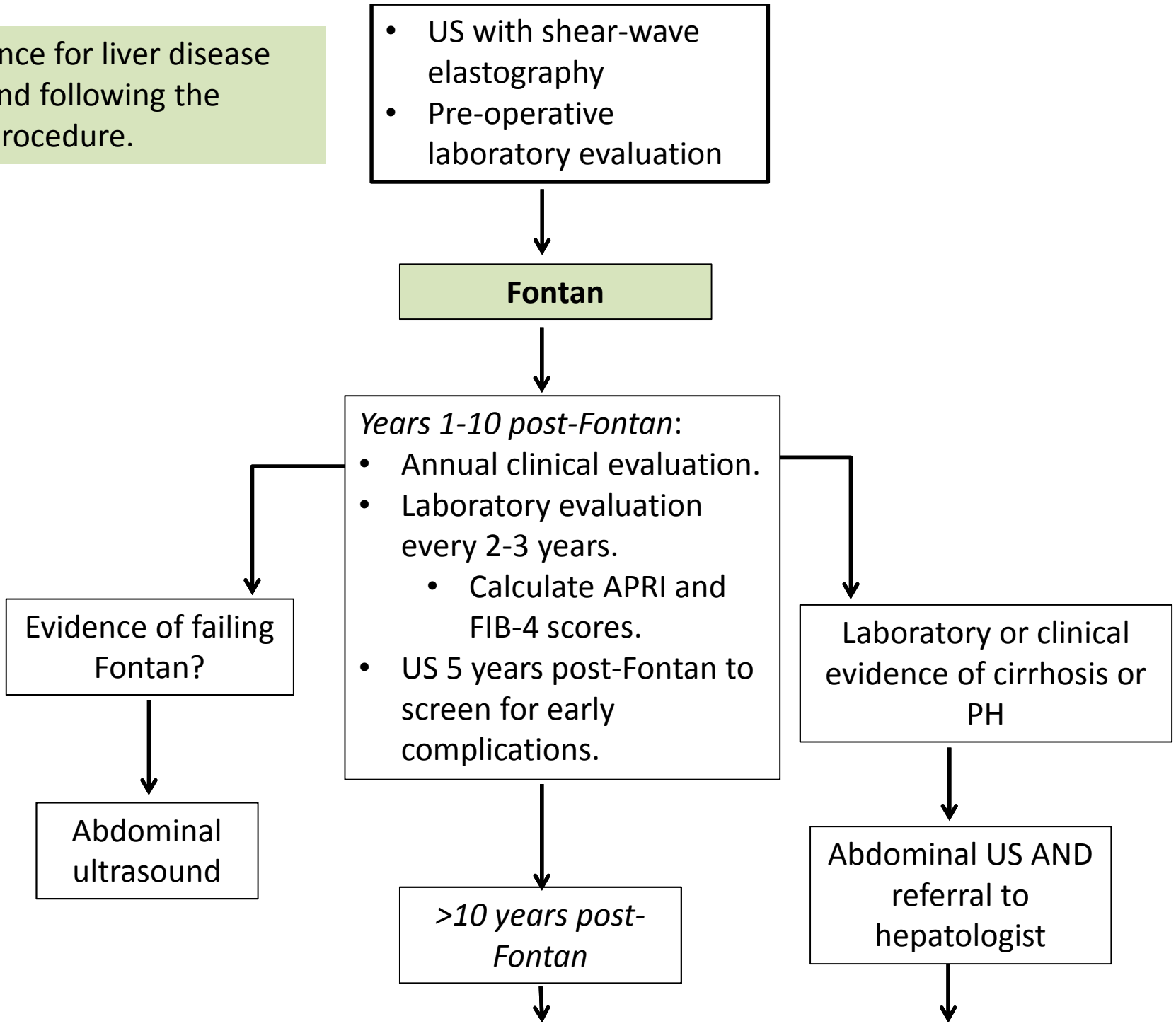
Proposed Recommendations for Liver Evaluation in Pts. with Functional Single Ventricle Physiology

- Searching for evidence-based surveillance and management of post-Fontan hepatic complications
- When, what tests ?
- If you find something, then what ?

Surveillance for liver disease ***before*** and following the Fontan procedure.



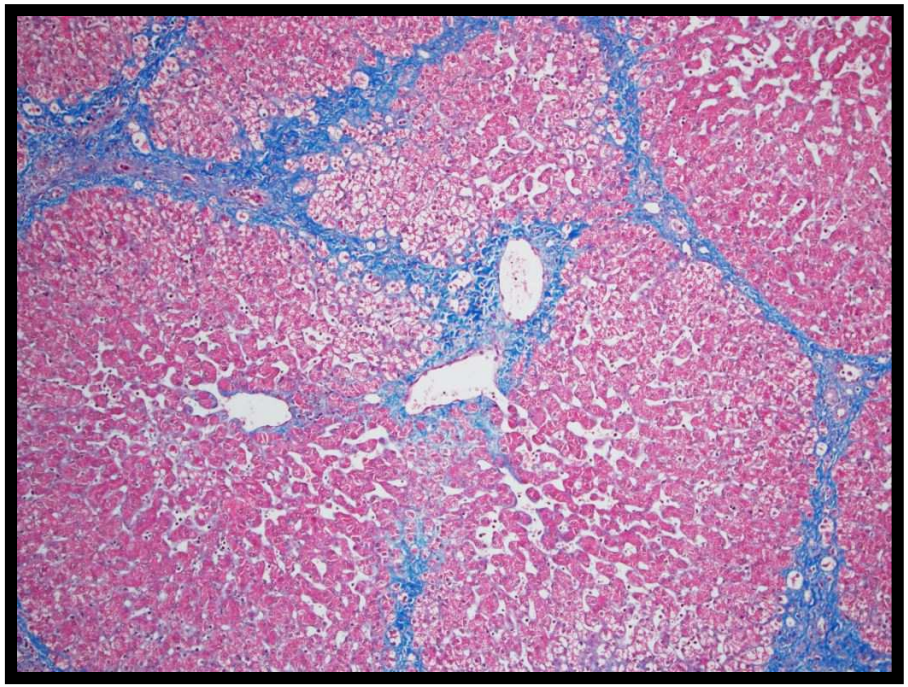
Moving Toward an Animal Model for FALD …

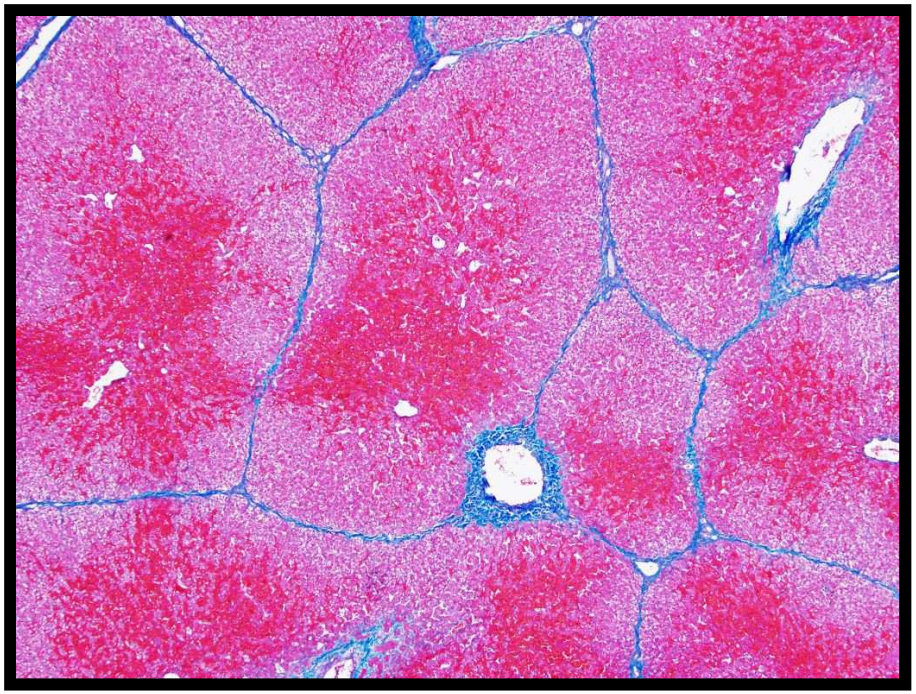
Porcine Pilot Study for Liver Disease

- Wanek Program large animal model for RV dysfunction (PA band +/- Cork) creates hepatic disease similar to that seen in FALD
- Acute fluid bolus & hydration status influence u/s shear wave measurement of liver stiffness
- Static and dynamic component to hepatic fibrosis & congestion
- Next steps … cath/USW correlation, ? Rx

P552

Moderate Fibrosis & Severe Congestion





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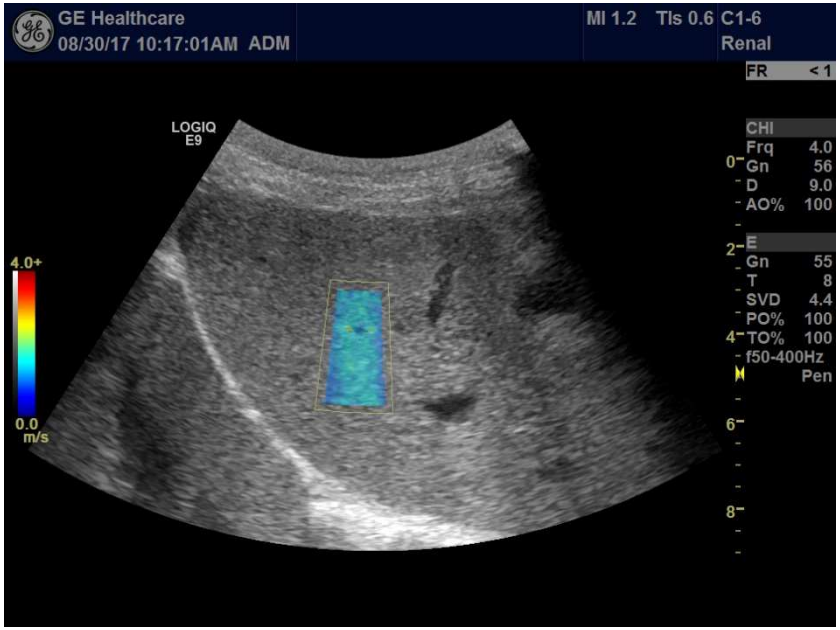
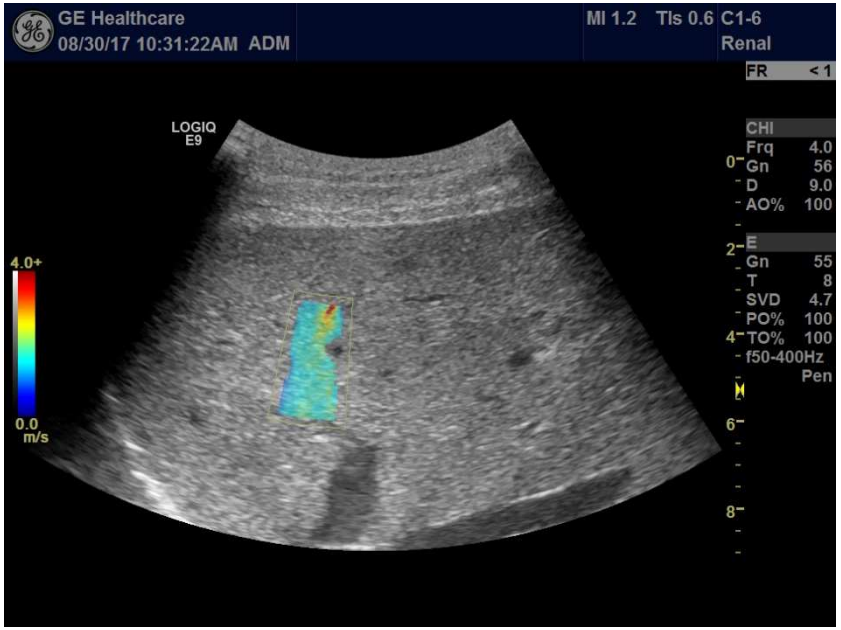
Pre-Bolus



Post-Bolus

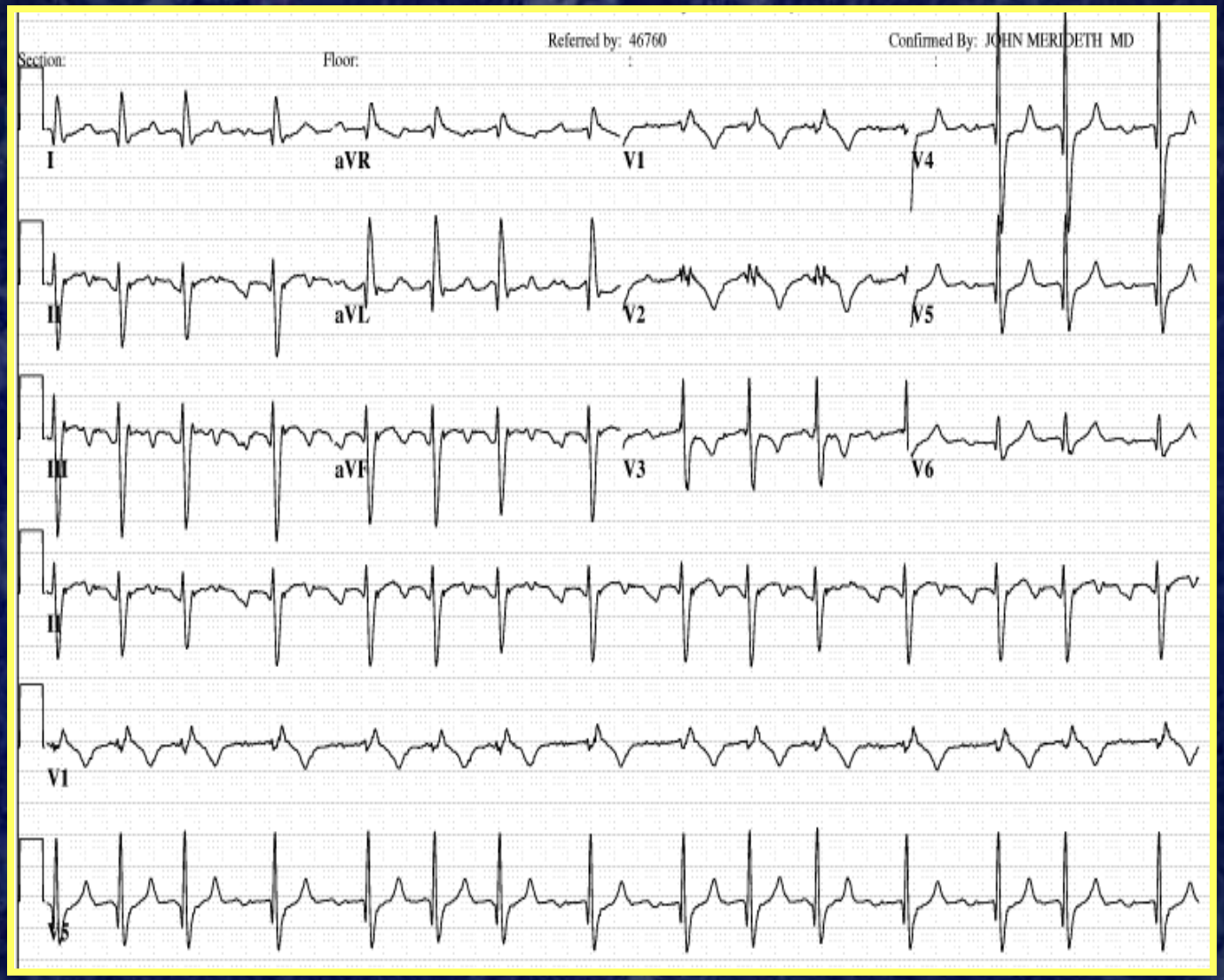


Path + Ultrasound shear modulus changes with fluid bolus

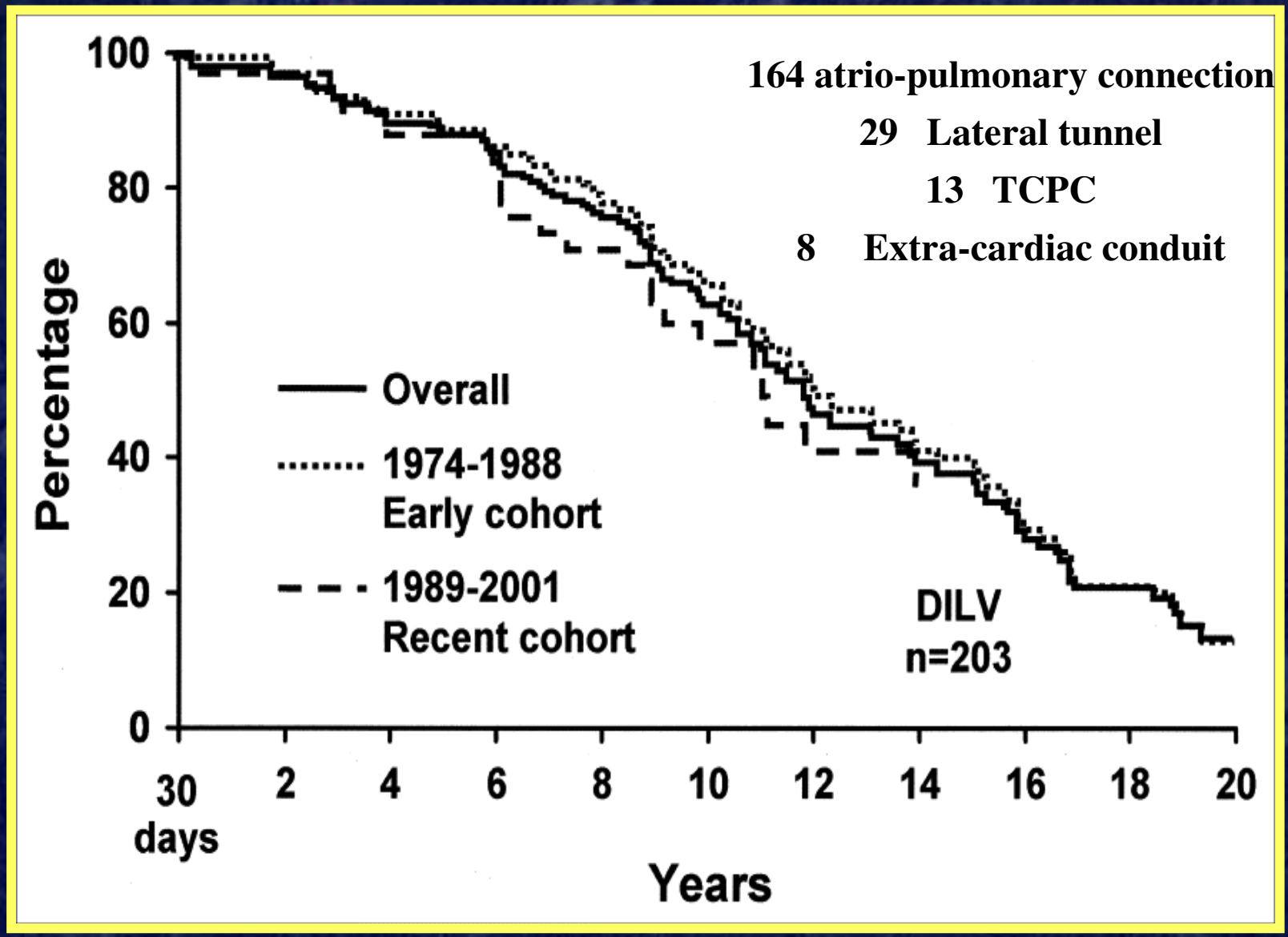
Pig #	Fibrosis/Vascular Congestion	% ↑shear modulus
P551	Moderate/Moderate	152%
P552	Moderate/Severe	died early
P553	Mild/Mild	127%
P554*	None/None	115%

* PA band but *not* corked

After Fontan, aging brings this …



Freedom from SVT after Fontan for DILV



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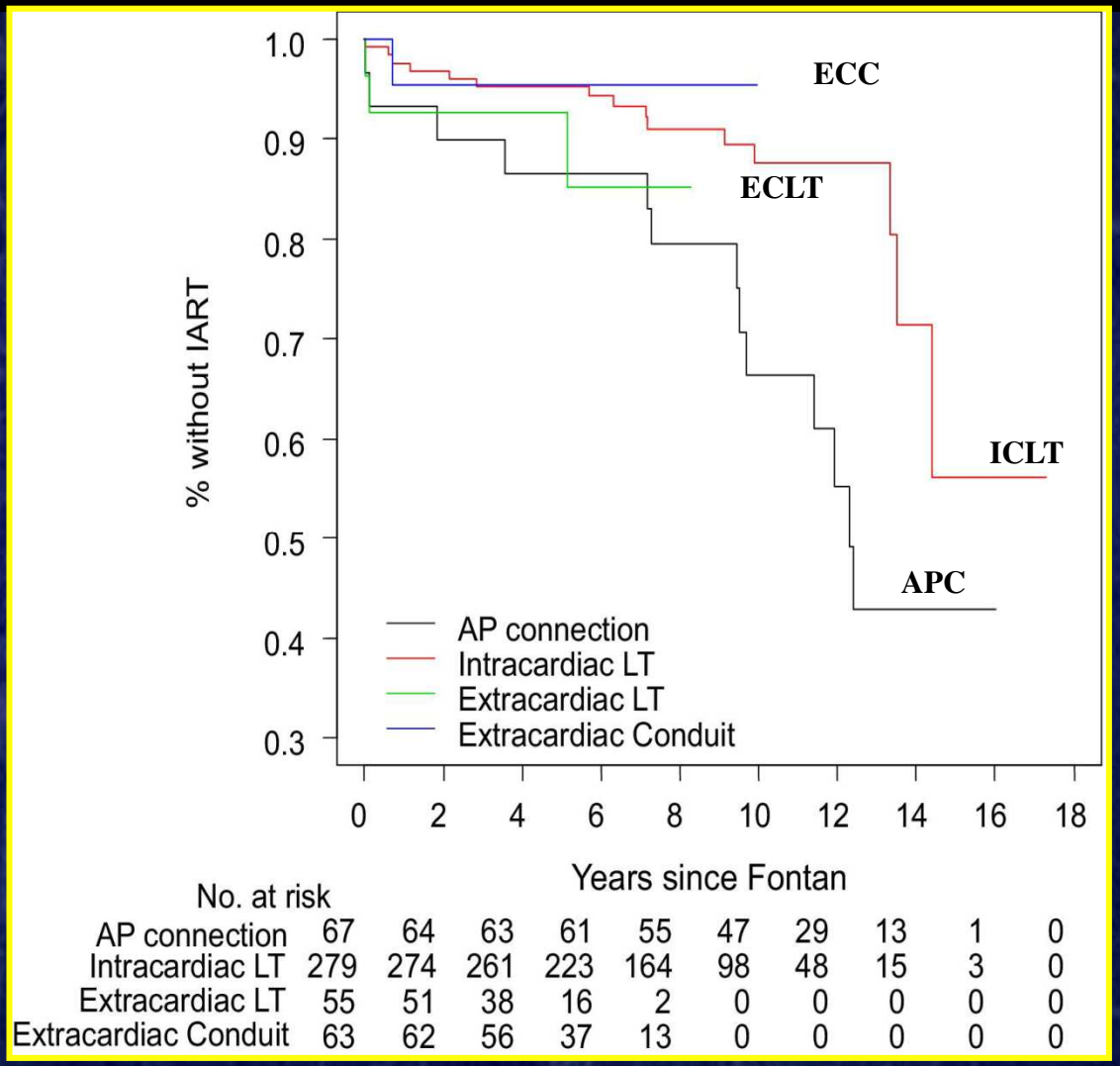
Earing , Cetta, Driscoll, et al , AJC, 2004

Freedom from IART after Fontan Operation by Type of Connection



No. at risk

AP connection	67	64	63	61	55	47	29	13	1	0
Intracardiac LT	279	274	261	223	164	98	48	15	3	0
Extracardiac LT	55	51	38	16	2	0	0	0	0	0
Extracardiac Conduit	63	62	56	37	13	0	0	0	0	0

Stephenson, et al, *JACC* 2010

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ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Sudden cardiac death and late arrhythmias after the Fontan operation

Kavitha N. Pundi, MD[1] | Krishna N. Pundi, MD[2] | Jonathan N. Johnson, MD[1,3] | Joseph A. Dearani, MD[4] | Zhuo Li, BS[5] | David J. Driscoll, MD[1] | Philip L. Wackel, MD[1] | Christopher J. McLeod, MD, PhD[3] | Frank Cetta, MD[1,3] | Bryan C. Cannon, MD[1,3]

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Funding Information
This study was funded by an internal grant from the Mayo Clinic College of Medicine.

Abstract

Objectives: We sought to examine the incidence and predictors of arrhythmias and sudden cardiac death (SCD) after Fontan operation.

Background: Arrhythmias and SCD have been reported following operations for congenital heart disease, but the incidence and risk factors have not been well defined in patients after a Fontan operation.

Methods: We reviewed records of all patients who had a Fontan operation from 1973 to 2012 ($n = 1052$) at our institution. A questionnaire was mailed to patients who were not known to be deceased at the initiation of the study. Late arrhythmias were classified as bradyarrhythmias or tachyarrhythmias requiring treatment >30 days after operation.

Results: We included 996/1052 (95%) patients with no arrhythmia diagnosis prior to Fontan. Overall 10-, 20-, and 30-year freedom from arrhythmias was 71%, 42%, and 24%, respectively. Of 864 patients who survived >30 days after Fontan, 304 (35%) had atrial flutter, 161 (19%) had atrial fibrillation, 108 (13%) had atrial tachycardia, 37 (4%) had reentrant supraventricular tachycardia, 40 (5%) had ventricular tachycardia, and 113 (13%) had sinus node dysfunction. Predictors of late arrhythmias included an atriopulmonary Fontan, age at operation (>16 years) or atrial arrhythmias postoperatively. During follow-up, 52/1052 (5%) patients had SCD, with 51 having documentation available; 8 patients died suddenly within 30 days and the remaining 43 had an average time to SCD of 6.9 ± 6.7 years (median was 3.8 years). Arrhythmias were documented in 28/43 (65%) patients prior to SCD. Predictors of SCD included atrioventricular valve replacement and post-bypass Fontan pressures >20 mm Hg; preoperative sinus rhythm was protective.

Conclusions: Arrhythmias and SCD are significant concerns among Fontan patients and specific risk factors may warrant closer follow-up and earlier consideration for therapy.

KEYWORDS
arrhythmias, Fontan, ICD, pacemaker, sudden cardiac death

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Conclusions: Arrhythmias and SCD are significant concerns among Fontan patients and specific risk factors may warrant closer follow-up and earlier consideration for therapy.

KEYWORDS
arrhythmias, Fontan, ICD, pacemaker, sudden cardiac death

5-7 %

- AVV replacement
- Fontan > 20 mmHg

NSR = protective

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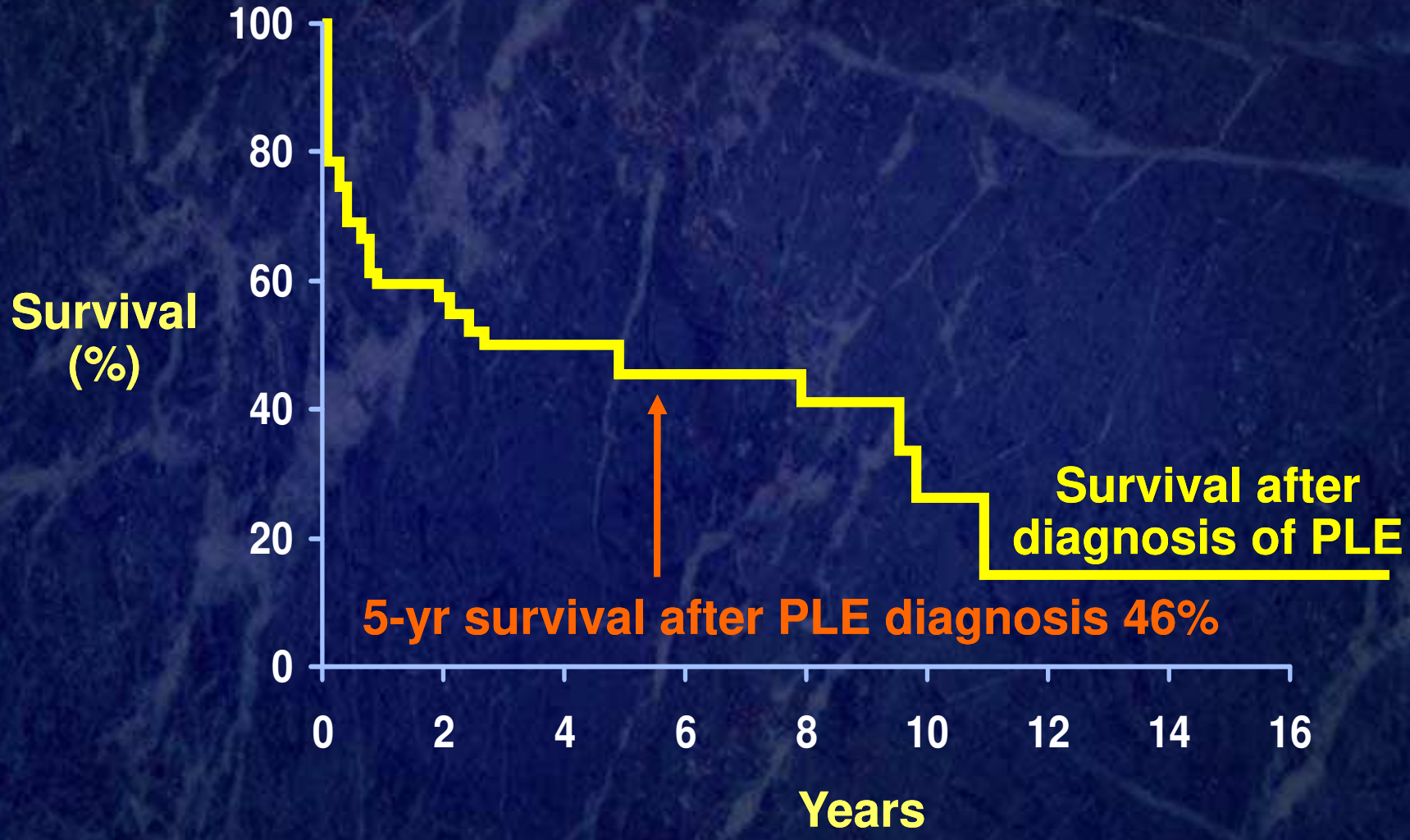
Sudden Cardiac Death after Fontan

- 1052 patients with 426 deaths
  - 43/426 (10%) deaths were SCD
  - Age: 20.5 ± 10.1 yrs
  - Duration from Fontan: 6.9 ± 6.7 yrs
  - 10-, 20-, and 30-year incidence of SCD:
    - 4.6%, 6.2%, and 7.1%
  - 28/43 (65%) had arrhythmias prior to SCD
    - vs. 41% in overall Fontan cohort (p = 0.0018)

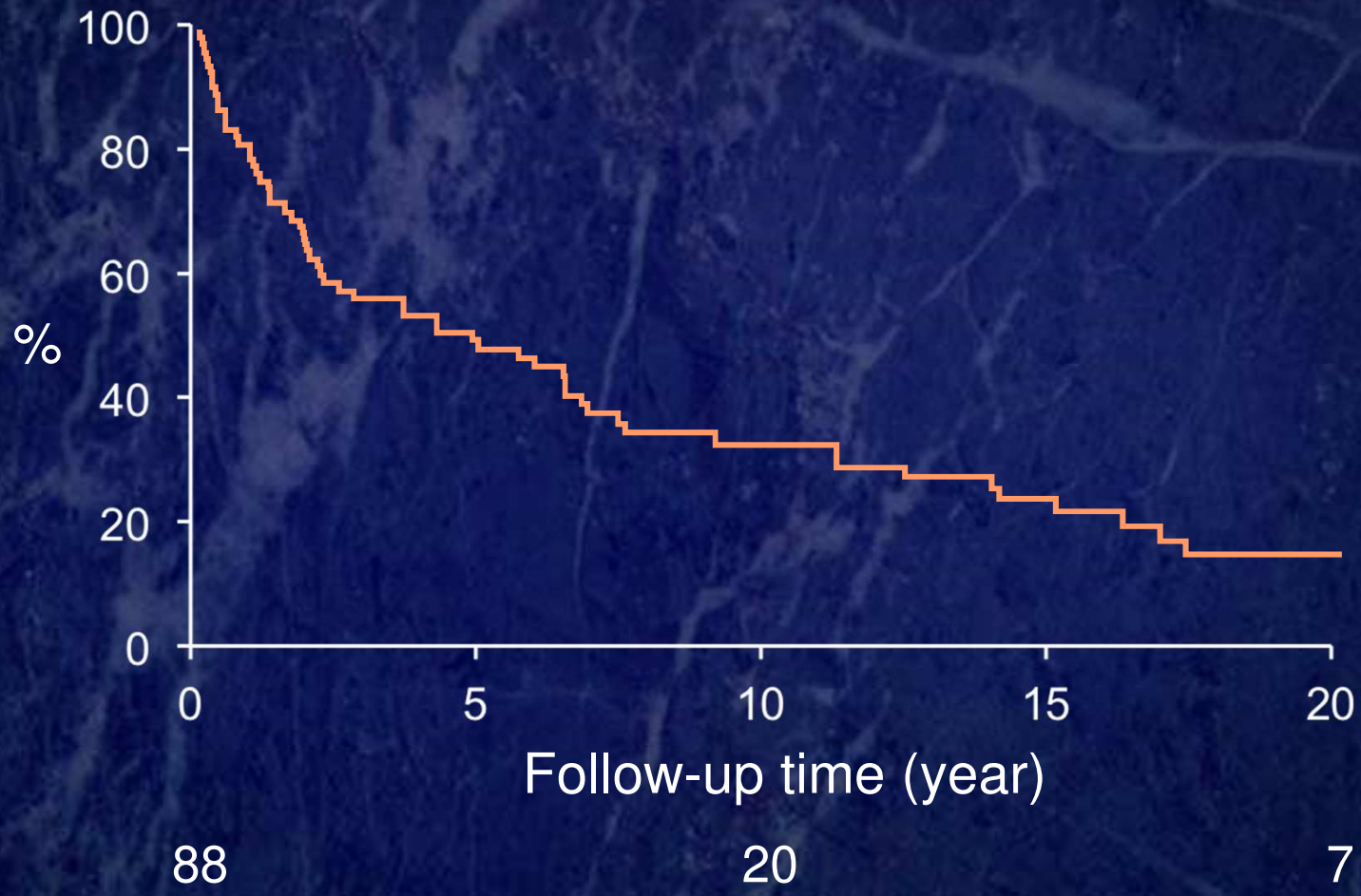
Fontan Survival with PLE



Feldt et al: JTCVS 1996 112:672

CP1061817-8

Transplant-free Survival After Diagnosis of PLE



Pundi et al: *J Am Coll Cardiol* 2015; 66:1700

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Clinical Outcomes and Improved Survival in Patients With Protein-Losing Enteropathy After the Fontan Operation

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ABSTRACT

BACKGROUND Patients with protein-losing enteropathy (PLE) following the Fontan operation have a reported 50% mortality at 5 years after diagnosis.

OBJECTIVES The aim of this study was to review outcomes in patients with PLE following the Fontan operation.

METHODS From 1992 to 2010, 42 patients (55% male) with PLE following the Fontan operation were identified from clinical databases at the Mayo Clinic. Data were collected retrospectively.

RESULTS Mean age at PLE diagnosis was 18.9 ± 11.0 years. Initial Fontan operation was performed at 10.1 ± 10.8 years of age. Mean time from Fontan operation to PLE diagnosis was 8.4 ± 14.2 years. Survival was 88% at 5 years. Decreased survival was seen in patients with high Fontan pressure (mean >15 mm Hg; p = 0.04), decreased ventricular function (ejection fraction <55%; p = 0.03), and New York Heart Association functional class >2 at diagnosis (p = 0.04). Patients who died had higher pulmonary vascular resistance (3.8 ± 1.6 Wood units [WU] vs. 2.1 ± 1.1 WU; p = 0.017), lower cardiac index (1.6 ± 0.4 l/min/m^2 vs. 2.7 ± 0.7 l/min/m^2; p < 0.0001), and lower mixed venous saturation (53% vs. 66%; p = 0.01), compared with survivors. Factors were assessed at the time of PLE diagnosis. Treatments used more frequently in survivors with PLE included spironolactone (21 [68%]), octreotide (7 [21%]), sildenafil (6 [19%]), fenestration creation (15 [48%]), and relief of Fontan obstruction (7 [23%]).

CONCLUSIONS PLE remains difficult to treat; however, in the current era, survival has improved with advances in treatment. Further study is needed to better understand the mechanism of disease and ideal treatment strategy.
(J Am Coll Cardiol 2014;64:54–62) © 2014 by the American College of Cardiology Foundation.

Protein-losing enteropathy (PLE) occurs in 5% to 15% of patients after the modified Fontan operation and has been a historically difficult complication to treat (1,2). PLE is characterized by the enteric loss of proteins such as albumin, immunoglobulins, and clotting factors. The protein loss that occurs leads to the clinical findings of peripheral edema, ascites, diarrhea, weight loss, and malabsorption. The exact mechanisms of this complication are poorly understood, and treatment strategies vary.

Patients with PLE following the Fontan operation have a reported 50% mortality at 5 years after initial diagnosis (1,2). Numerous treatment strategies have been used, including medical therapy, such

SEE PAGE 63

as controlled-release budesonide and sildenafil, as well as interventional and surgical therapies, such as Fontan revision and Fontan fenestration creation (3–6). Even with these treatment advances, limited studies have reported improved survival

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5 yr. survival = 88%

Worse outcome: Mean PAP > 15 mmHg EF < 55%

Non-Cohort Study

MAYO CLINIC

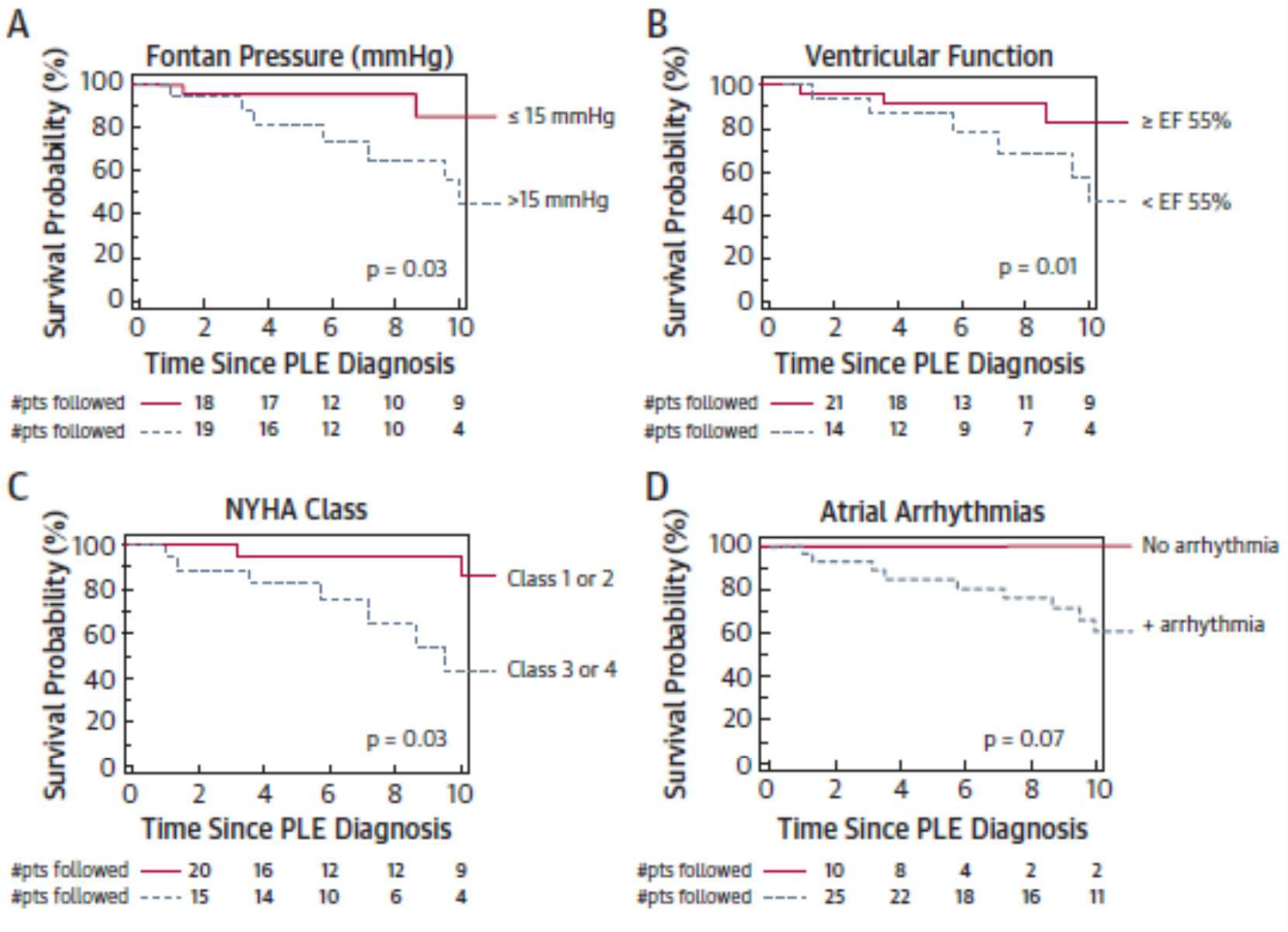

FIGURE 2 **Factors Affecting Survival in Patients With PLE After the Fontan Operation**

Fontan pressure <15 mm Hg **(A)**, ventricular function >55% **(B)**, and New York Heart Association (NYHA) functional class III or IV **(C)** at time of diagnosis were associated with decreased survival. The presence of atrial arrhythmias **(D)** was also associated with decreased survival, although this association was not statistically significant. EF = ejection fraction; other abbreviation as in Figure 1.

Contraception Practices and Pregnancy Outcome in Patients after Fontan Operation

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ABSTRACT

Objective. The feasibility and safety of pregnancy after the Fontan operation is not well understood. We sought to determine contraception practices and early and late outcomes of pregnancy after the Fontan operation.

Design. We performed a retrospective review of medical records to identify women of childbearing age from the Mayo Clinic Fontan database. A follow-up questionnaire was mailed to all patients not known to be deceased at the time of study. Patients with available contraception and pregnancy data were included in the study.

Results. Of the 138 women with available contraception data, 44% used no contraception, 12% each used barrier methods, combination hormone therapy or sterilization, 8% used Depo-Provera, 7% had intrauterine devices, 4% had a partner with a vasectomy and 1% used progestin pills. Six women had thrombotic complications (only one using oral contraceptives). Thirty-five women had pregnancy data available. Prior to the Fontan operation there were 10 pregnancies (8 miscarriages, 2 therapeutic abortions, and no live births). After the Fontan operation there were 70 pregnancies resulting in 35 miscarriages (50%), 29 live births (41%), and 6 therapeutic abortions (9%). There were no maternal deaths during pregnancy. During long-term follow up (26 ± 6 years since the Fontan), 1 death, and 1 cardiac transplant occurred. Mean gestational age of the newborns (n = 22/29) was 33.1 ± 4.0 weeks; mean birth weight (n = 20/29) was 2086 ± 770 g. There was 1 neonatal death because of prematurity and two children were born with congenital heart disease (one patent ductus arteriosus and one membranous ventricular septal defect).

Conclusions. Pregnancy after the Fontan operation is associated with a high rate of miscarriages, preterm delivery, and low birth weight. Further studies are needed to identify specific variables influencing risk stratification of pregnancy in this patient population.

Key Words. Fontan Operation; Contraception; Pregnancy; Miscarriage; Abortion; Prematurity

Introduction

Since its introduction in 1971, the Fontan operation has become the definitive palliation for patients with a functional univentricular heart.[1,2] Over the past 40 years, overall survival and long-term outcomes have improved. However, there are important long-term sequelae such as the development of ventricular failure, thromboembolism, arrhythmias, cirrhosis, and protein losing enteropathy (PLE).[3–8]

Historically, women who had a Fontan operation were advised to refrain from pregnancy.[9] However, as more women after the Fontan operation survive into adulthood, there have been case series of successful pregnancies. Data from a limited number of case series have shown that pregnancy in this patient population continues to pose a significant risk to mother and baby.[9,10] We

Funding sources: This study was funded by an internal grant from the Mayo Clinic College of Medicine.

Pregnancy after Fontan

Study	No. Woman	Maternal Age @ Pregnancy (yrs)	No. of Pregnancy	Preterm % Mean GA Mean BW (kg)	Maternal Deaths *During*	Maternal Deaths *After*	Anti-coagulation During Pregnancy	Ventricular Morphology
Mayo *Pundi et al 2016*	35	26 (18-36)	70	81% 33 wks (2.1)	0	1	aspirin – 12 LMWH – 3 VKA - 0	LV – 68%
France *Gouton et al 2015*	37	27 (19-41)	59	69% 34 wks (2.0)	0	0	aspirin – 11 LMWH/UFH – 17 VKA - 10	LV – 70%
No. Am. *Cannobio et al 2013*	52	25 (17-36)	103	- 34 wks (2.2)	0	5	aspirin – 52 LMWH – 4 VKA - 4	-
ANZ *Zenter et al 2016*	20	25 (23-32)	40	72% 31 wks (1.6)	0	0	Aspirin - 6 LMWH/VKA - 5	-

Pregnancy after Fontan

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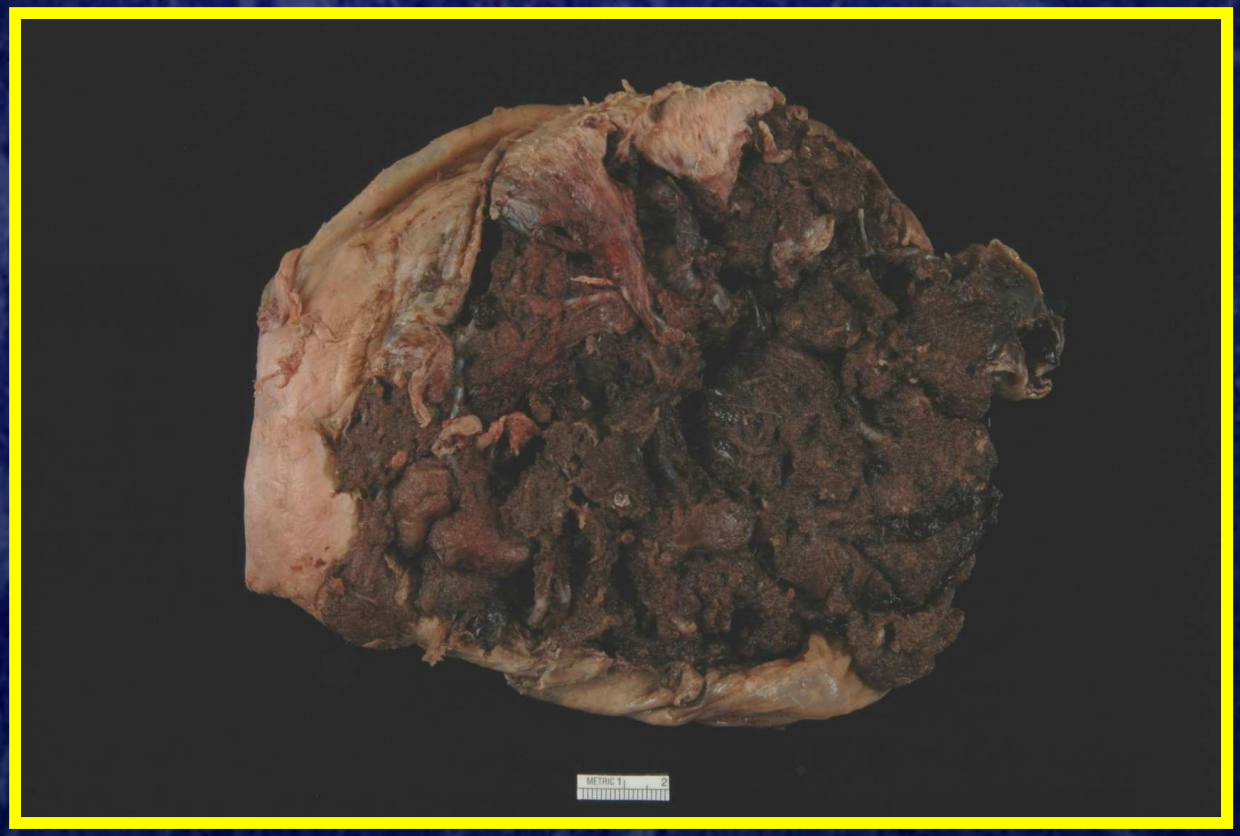
ANZ *Zenter et al 2016*	20	25 (23-32)	40	72% 31 wks (1.6)	0	0	Aspirin - 6 LMWH/VKA - 5	-

Placenta: 27 week delivery - preeclampsia
30 y/o with tricuspid atresia, s/p Fontan
850 gm male newborn



Casey 4 years later …

Viable Pregnancies after Fontan

- ***All*** **women with viable pregnancies had:**
  - **EF > 40%**
  - **Systemic oxygen saturation > 90%**

- **No maternal deaths or thrombotic events**
  - **1 death: 11 yrs after successful pregnancy (cause unknown)**
- **Pregnancy outcome did not correlate with postop Fontan pressures**

Advice for Women after Fontan re. Pregnancy

Fertility and pregnancy in the Fontan population☆

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ABSTRACT

Background: Women with a Fontan circulation are deemed at significantly increased risk of maternal morbidity and mortality during pregnancy. Publications describe a small number of pregnancies worldwide and a high rate of miscarriage. We compiled the experience of women enrolled in the Australia and New Zealand Fontan (ANZ) Registry with regard to menarche, contraceptive use, pregnancy advice and pregnancy outcomes.
Methods: Women within the ANZ Fontan Registry were contacted and asked to consent to receiving sequential questionnaires.
Results: 156 women ≥ 18 years of age (including 4 deceased individuals) were identified, 101 women consented and 97 completed the initial questionnaire. Women were aged (median) 25 years (23–32); menarche occurred at a median 14 years (13–16). A wide variety of contraceptive methods was reported. 81% of women reported having received advice that pregnancy carried an increased risk or was inadvisable. Pregnancy was reported in a minority (n = 27). Miscarriage (42.5%) and termination (7.5%) accounted for half the pregnancy outcomes and the babies were born early (median 31.5 weeks) and small (median 1350 g). Maternal complications of bleeding, arrhythmia and heart failure were reported with no early maternal mortality.
Conclusions: In women with a Fontan circulation the fertility onset is delayed and pregnancy has a higher rate of miscarriage. Successful pregnancy resulted in small and premature babies. Significant maternal morbidity occurred. Whether pregnancy with its volume loading has an adverse effect on the long-term outcome of women with a single ventricle remains to be elucidated.

Table 4
Pregnancy advice.

Pregnancy advice	Number of women (%)
No advice provided	6 (6%)
Pregnancy would be all right	9 (9%)
Pregnancy would be all right to at increased risk	3 (3%)
Pregnancy would be at increased risk	42 (43%)
Pregnancy would be at increased risk to inadvisable	12 (12%)
Pregnancy would be inadvisable	25 (26%)

This table presents the reported medical advice given to this cohort of women regarding their capacity to undergo pregnancy.

Fontan & Pregnancy

- Select women after Fontan can have successful pregnancies
- Low maternal mortality, some morbidity
- Pre-term birth *(> 65%)* and obstetrical complications are *common*
- Require rigorous pre-pregnancy evaluation and care at highly specialized centers
- *Placenta –*
  - *Another site of end-organ damage?*

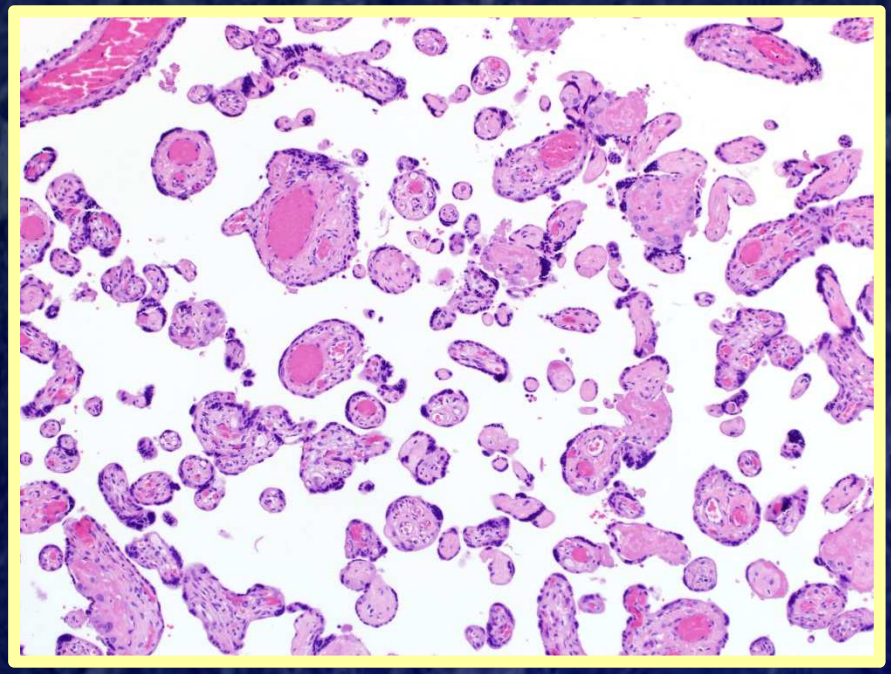
The Placenta

- End-organ effected by Fontan hemodynamics
- Factors effecting the placenta:
  - Low cardiac output
  - Maternal hypoxemia
  - Elevated central venous pressure
- May contribute to:
  - Placental thrombosis, ischemia

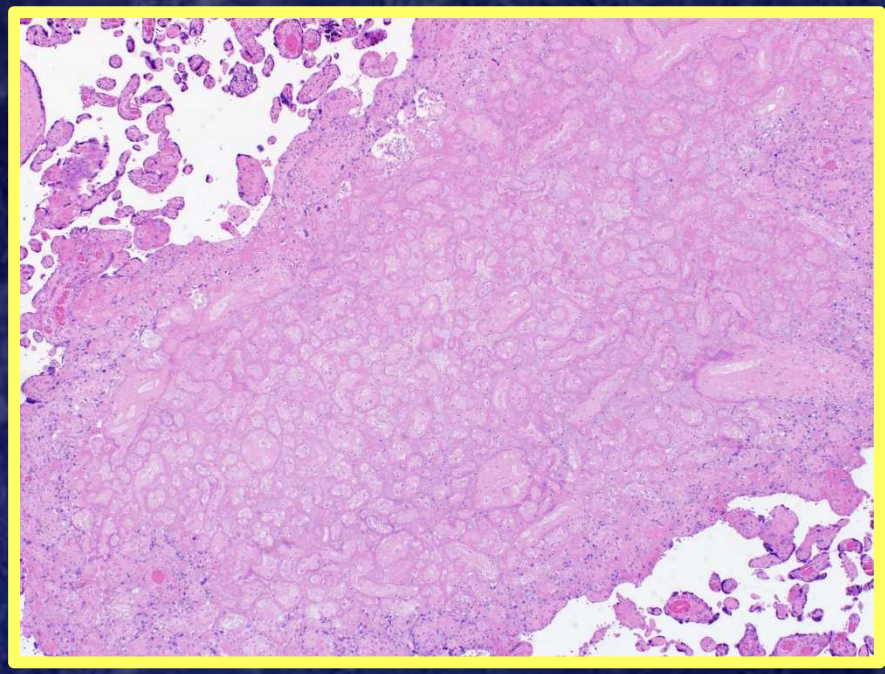
Placental Insufficiency

- Pre-eclampsia
- Oligohydramnios
- Miscarriage
- Stillbirth
- Pre-term delivery
- SGA newborns

- *May also be factors in fetus with CHD*

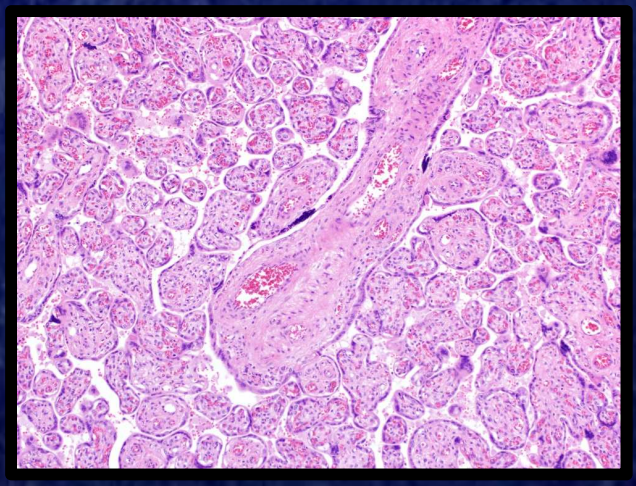


Villous Hypoplasia



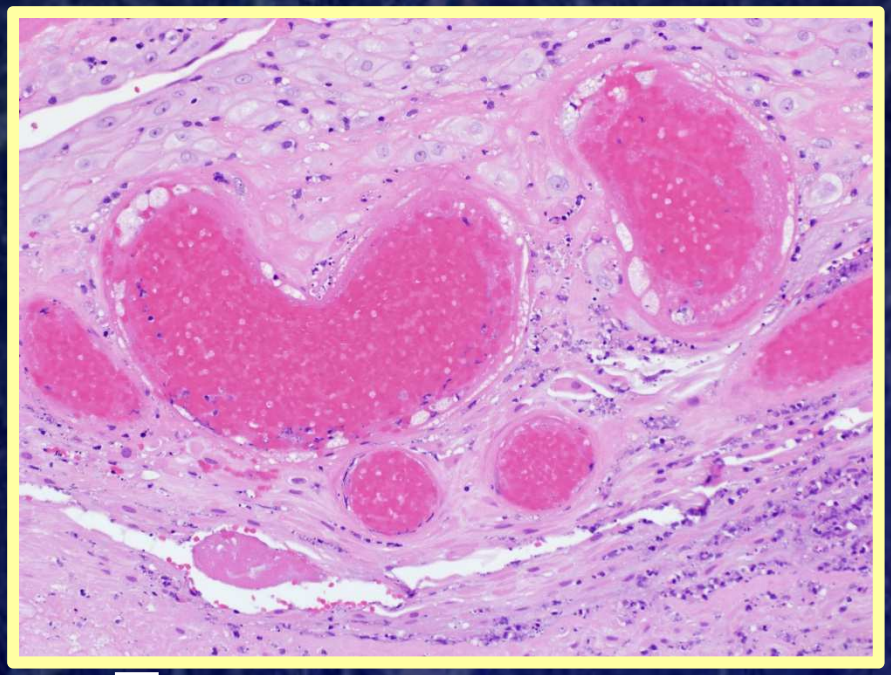
Placental Infarct

Chorionic Villi in Pre-eclampsia

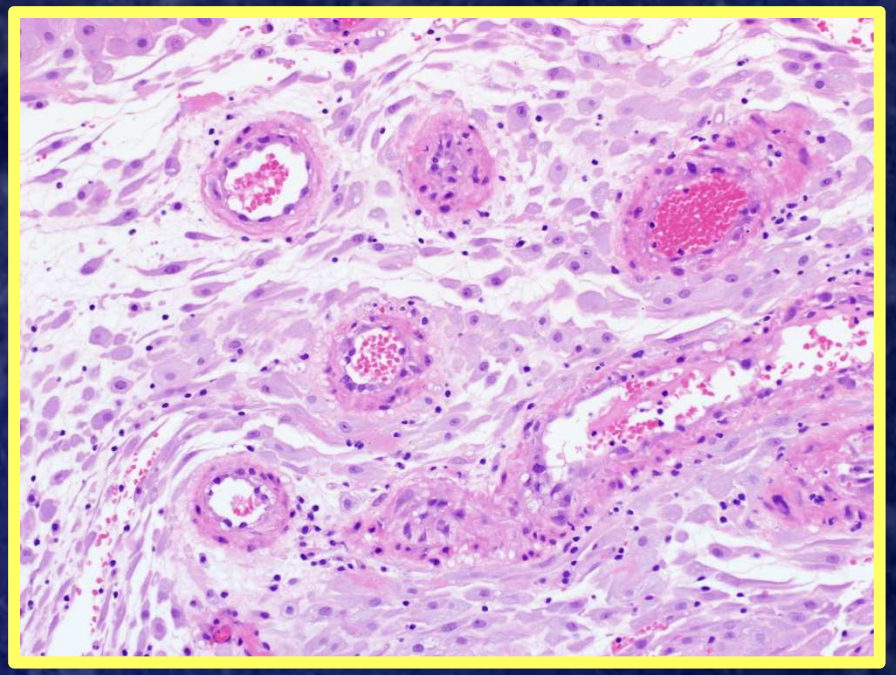


Normal

Courtesy of Sarah Kerr, MD

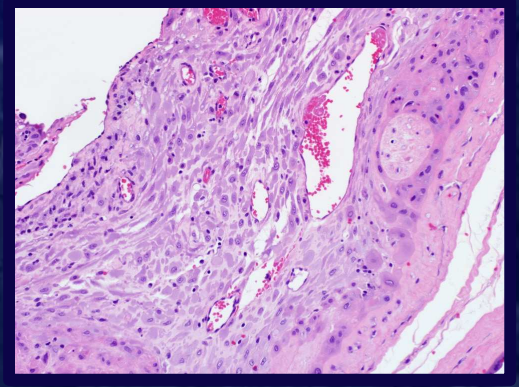


Foamy histiocytes



Thickened spiral arteries

Decidual Vessels in Pre-eclampsia



Normal

Courtesy of Sarah Kerr, MD

Placental Evidence of Pre-eclampsia

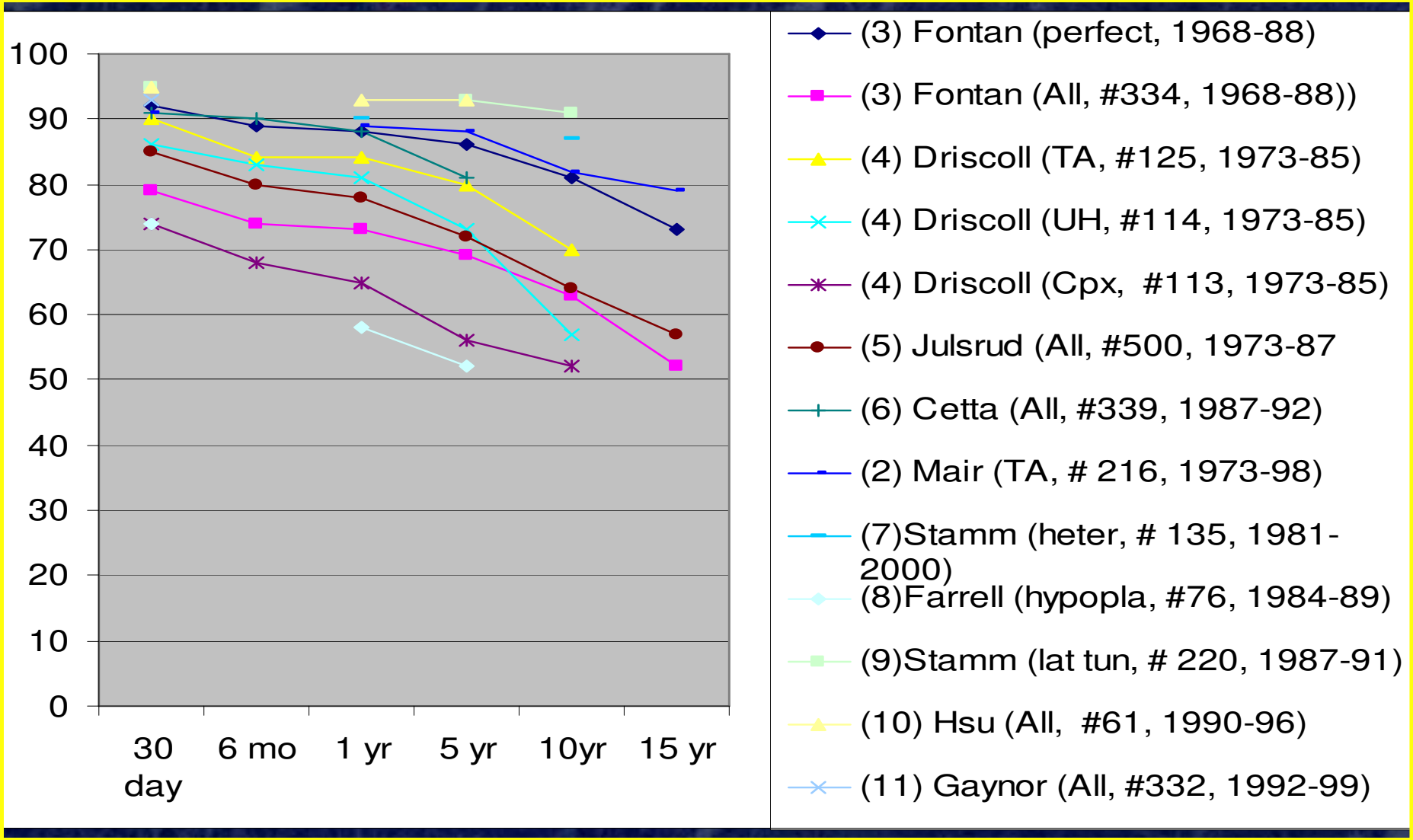
- Chorionic Villi:
  - Hypoplasia with ↑ syncytial knotting
  - Infarction

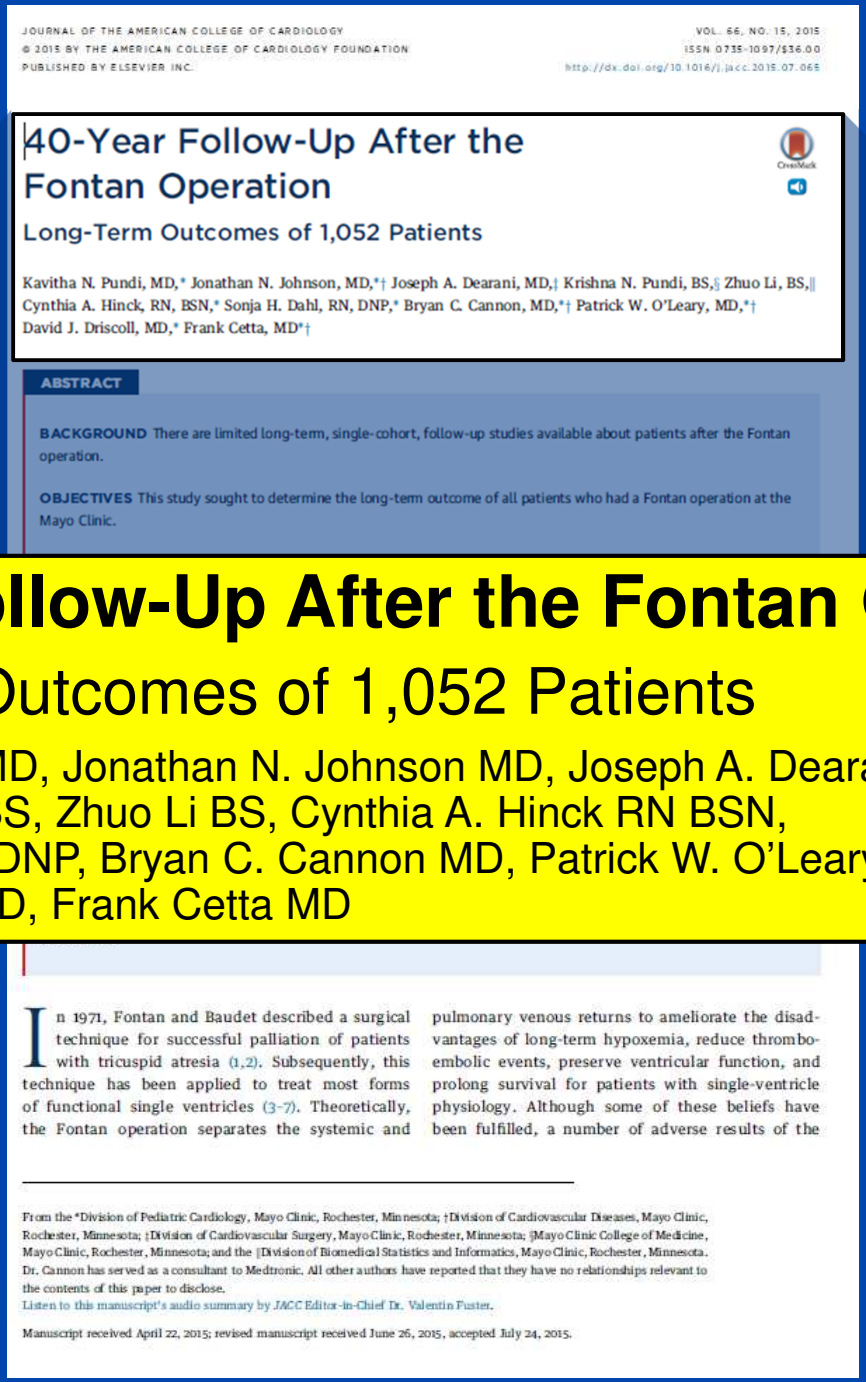
- Decidual Vessels:
  - Hypertrophic vasculopathy
    - Thickened vessel walls
  - Foamy histiocytes … fibrinoid necrosis
  - Acute atherosis

Parameters Related to Successful *Pregnancy* after Fontan

- Normal systolic & diastolic function
- Low PA pressure and resistance
- Only mild AV valve regurgitation
- No obstruction:
  - Fontan, PAs, PV, outflow tract, aorta
- Sinus rhythm
- Systemic arterial saturation > 90%
- EF > 40%

Survival after Fontan Operation





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40-Year Follow-Up After the Fontan Operation

Long-Term Outcomes of 1,052 Patients

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ABSTRACT

BACKGROUND There are limited long-term, single-cohort, follow-up studies available about patients after the Fontan operation.

OBJECTIVES This study sought to determine the long-term outcome of all patients who had a Fontan operation at the Mayo Clinic.

40-Year Follow-Up After the Fontan Operation

Long-Term Outcomes of 1,052 Patients

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In 1971, Fontan and Baudet described a surgical technique for successful palliation of patients with tricuspid atresia (1,2). Subsequently, this technique has been applied to treat most forms of functional single ventricles (3–7). Theoretically, the Fontan operation separates the systemic and pulmonary venous returns to ameliorate the disadvantages of long-term hypoxemia, reduce thromboembolic events, preserve ventricular function, and prolong survival for patients with single-ventricle physiology. Although some of these beliefs have been fulfilled, a number of adverse results of the

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Dr. Cannon has served as a consultant to Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

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MAYO CLINIC

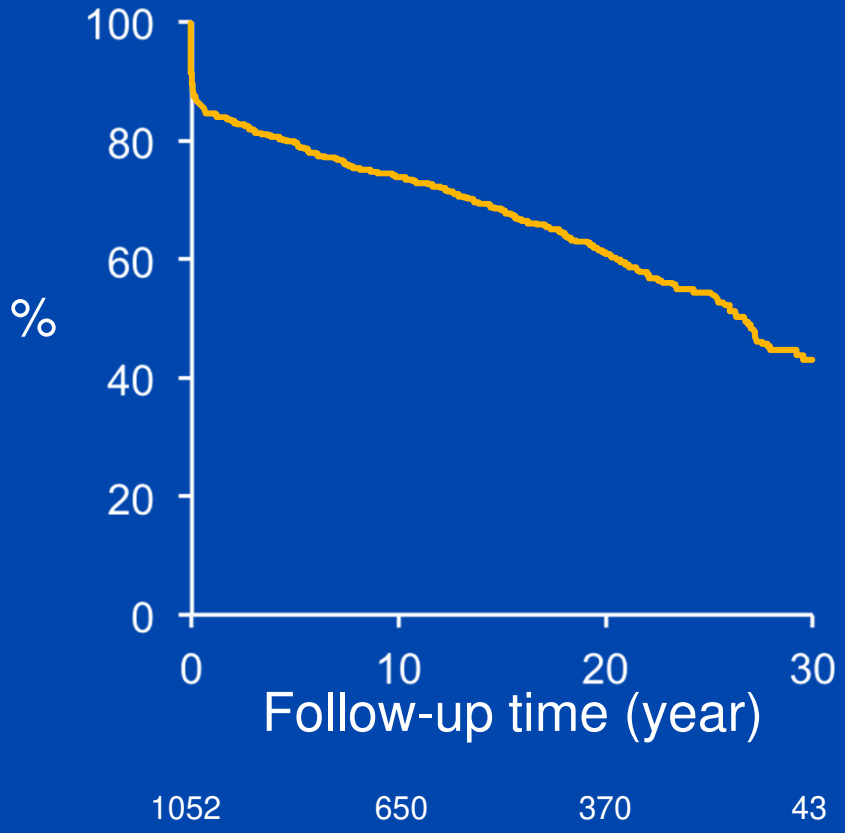
40 Years of the Fontan at Mayo

- October 1973 → June 2012
- 1052 patients had Fontan @ Mayo
- Median age @ Fontan = 7 yrs
  - 7 mos → 53 yrs
- Oldest survivor = *67* years old

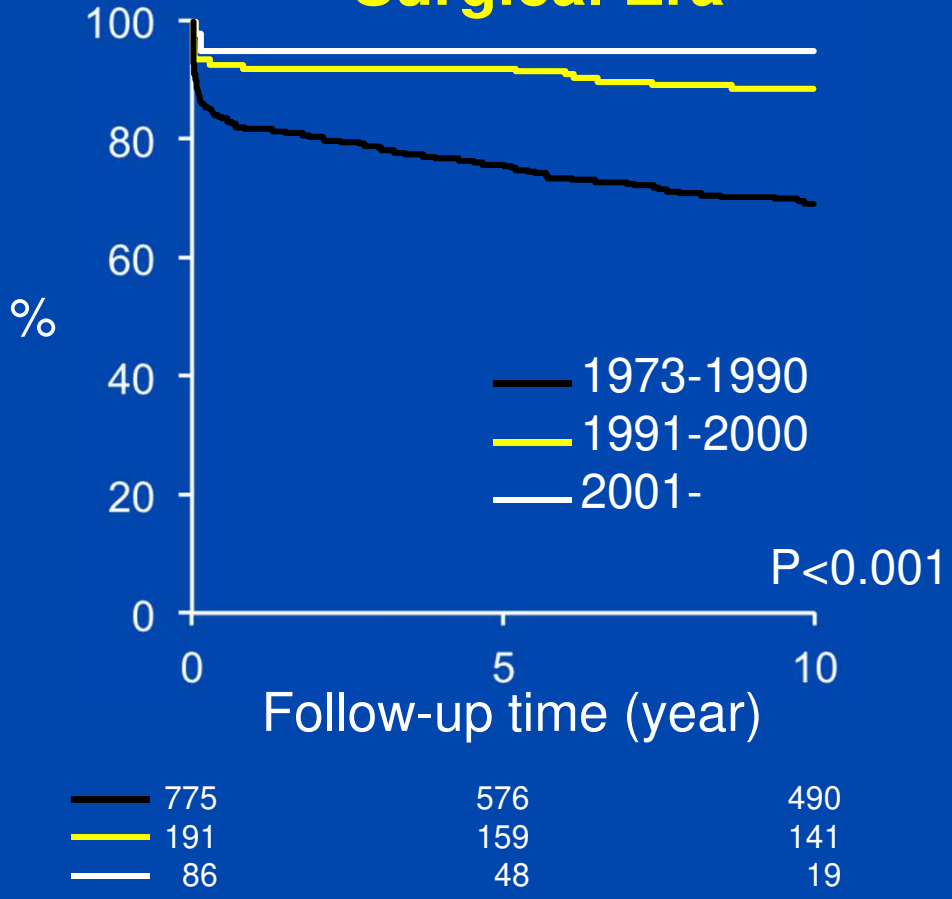
MAYO CLINIC

Survival after the Fontan Operation

Overall Survival



Survival by Surgical Era



Pundi et al: *J Am Coll Cardiol* 2015; 66:1700

MAYO CLINIC

Procedures after Fontan

N = 1052 pts

- Pacemaker/AICD 212 (20%)
- Fontan revision/conversion 117 (11%)
- AV valve repair/replacement 66 (5%)

For many, Fontan is *not* the end …

MAYO CLINIC

Longitudinal Outcomes of Patients With Single Ventricle After the Fontan Procedure

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ABSTRACT

BACKGROUND Multicenter longitudinal objective data for survival into adulthood of patients who have undergone Fontan procedures are lacking.

OBJECTIVES This study sought to describe transplant-free survival and explore relationships between laboratory measures of ventricular performance and functional status over time.

METHODS Exercise testing, echocardiography, B-type natriuretic peptide, functional health assessment, and medical history abstraction were repeated 9.4 ± 0.4 years after the Fontan Cross-Sectional Study (Fontan 1) and compared with previous values. Cox regression analysis explored risk factors for interim death or cardiac transplantation.

RESULTS From the original cohort of 546 subjects, 466 were contacted again, and 373 (80%) were enrolled at 21.2 ± 3.5 years of age. Among subjects with paired testing, the percent predicted maximum oxygen uptake decreased (69 ± 14% vs. 61 ± 16%; $p < 0.001$; n = 95), ejection fraction decreased (58 ± 11% vs. 55 ± 10%; $p < 0.001$; n = 259), and B-type natriuretic peptide increased (median [interquartile range] 13 [7 to 25] pg/ml vs. 18 [9 to 36] pg/ml; $p < 0.001$; n = 340). At latest follow-up, a lower Pediatric Quality of Life Inventory physical summary score was associated with poorer exercise performance (R^2 adjusted = 0.20; $p < 0.001$; n = 274). Cumulative complications since the Fontan procedure included additional cardiac surgery (32%), catheter intervention (62%), arrhythmia treatment (32%), thrombosis (12%), and protein-losing enteropathy (8%). Since Fontan 1, 54 subjects (10%) have received a heart transplant (n = 23) or died without transplantation (n = 31). The interval risk of death or/cardiac transplantation was associated with poorer ventricular performance and functional health status assessed at Fontan 1, but it was not associated with ventricular morphology, the subject's age, or the type of Fontan connection.

CONCLUSIONS Interim transplant-free survival over 12 years in this Fontan cohort was 90% and was independent of ventricular morphology. Exercise performance decreased and was associated with worse functional health status. Future interventions might focus on preserving exercise capacity. (Relationship Between Functional Health Status and Ventricular Performance After Fontan—Pediatric Heart Network; NCT00132782) (J Am Coll Cardiol 2017;69:2735–44)

PHN study

373 pts

90% Tx-free @ 12 yrs f/u

↓ Exercise performance with time

INTERNAL MEDICINE JOURNAL

The Australia and New Zealand Fontan Registry: description and initial results from the first population-based Fontan registry

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Key words
Fontan procedure, heart defect, congenital, registry, outcome assessment (healthcare), research design.

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Abstract

Background: The Fontan procedure is the final in a series of staged palliations for single-ventricle congenital heart disease, which encompasses rare and heterogeneous cardiac lesions. It represents an unusual and novel physiological state characterised by absence of a subpulmonary ventricle.

Aims: The population is growing steadily, prompting creation of this registry to study their epidemiology, demographic trends, treatment and outcomes.

Methods: This multicentre, binational, prospective and retrospective, web-based registry involving all congenital cardiac centres in the region has identified nearly all Fontan patients in Australia and New Zealand. Patients identified retrospectively were approached for recruitment. New recipients are automatically enrolled prospectively unless they choose to opt-out. Follow-up data are collected yearly.

Results: Baseline data were obtained in 1072 patients as at 1 January 2011. Ninety-nine patients died; 64 were lost to follow up. Forty-four per cent of patients lost were between 20 and 30 years of age. The size of the Fontan population is increasing steadily. Among 973 living patients, 541 (56%) gave consent for prospective collection of follow up. Between 1 January 2011 and 1 January 2013, an additional 47 subjects were enrolled prospectively. The current proportion of patients operated with hypoplastic left heart syndrome is currently 29% and is growing rapidly.

Conclusion: The population surviving after the Fontan procedure has been growing in recent decades, especially since survival with hypoplastic left heart syndrome has improved. The Australia and New Zealand Fontan Registry provides population-based data, and only large databases like this will give opportunities for understanding the population and performing prospective trials.

Population Based Outcomes

1072 pts

29% HLHS

REVIEW ARTICLE

WILEY Congenital Heart Disease

Five decades of the Fontan operation: A systematic review of international reports on outcomes after univentricular palliation

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Abstract

Almost fifty years after its first clinical application, the modified Fontan operation is among the most frequently performed procedures in congenital heart disease surgery in children today. The objective of this review is to systematically summarize the international evolution of outcomes in regard to morbidity and mortality of patients with Fontan palliation. All studies published over the past five decades with more than 100 Fontan patients included were screened. In eligible studies, information concerning preoperative patients' characteristics, Fontan modifications employed, early mortality, long-term survival and frequency of relevant complications was extracted. Ultimately, thirty-one studies published by the largest surgical centers with an overall number of 9390 patients were included in this review. The extracardiac total cavopulmonary anastomosis is the most frequently used Fontan modification. Hemodynamic data demonstrate a rigorous overall adherence to suggested Fontan selection criteria. The analysis showed a clear trend toward improved early and long-term survival over the time period covered. Although inconsistently reported, severe complications such as arrhythmias, thromboembolic events and protein-losing enteropathy as well as reoperations and reinterventions were frequent. In conclusion, patients palliated for complex univentricular heart malformations nowadays benefit from the experience and technical developments of the past decades and have a significantly improved long-term prognosis. However, important issues concerning postoperative long-term morbidity and mortality are still unsolved and clear intrinsic limitations of the Fontan circulation are becoming evident as the population of Fontan patients ages.

KEYWORDS

Fontan procedure, long-term outcome, single ventricle, univentricular heart disease

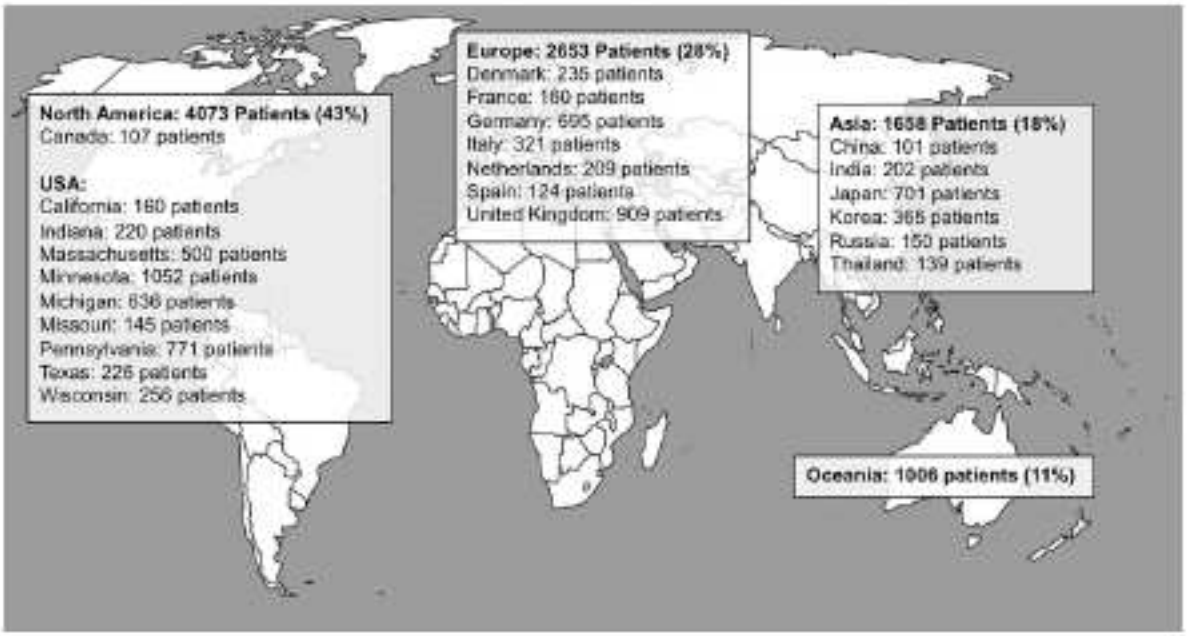

FIGURE 1 Overview of Fontan patient numbers and geographical distribution. Depiction of patient numbers and their geographical distribution from reports included in this review. Figures are absolute numbers and percentages of total patient number from the reports included

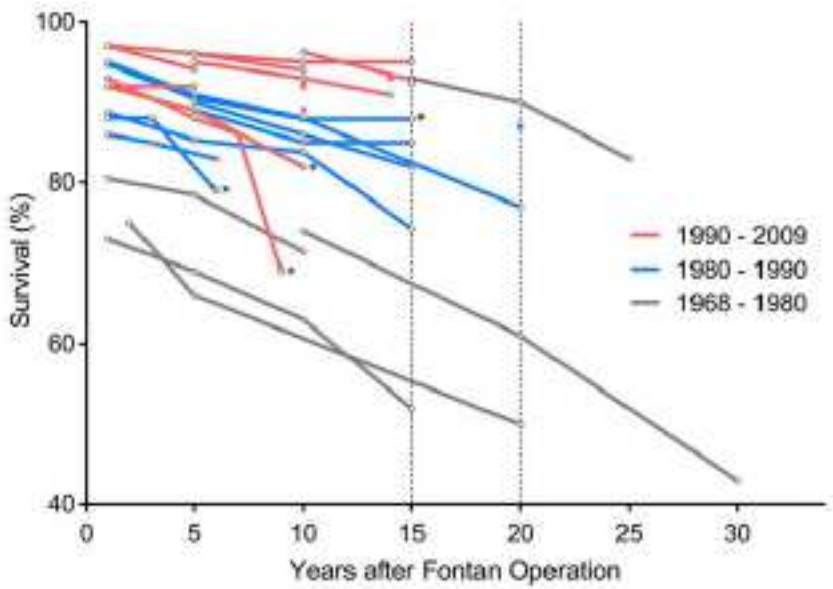

FIGURE 4 Long-term survival after Fontan. Reported late survival rates after definitive univentricular palliation of included studies according to study period covered. Only studies with specified survival rates are included in this figure. Dots represent respective reported Kaplan-Meier survival estimates at given time points. Connecting lines represent individual studies having survival estimates reported at several time points. Line/dot colors mark surgical eras, dashed vertical lines mark 15 and 20 years. *, definition by death and cardiac transplantation or revision

All Patients with Single Ventricle Physiology are *not* the Same

- Older studies:
  - Tri atresia, DILV
  - PA/IVS
- Heterotaxy:
  - over/under represented
  - more AV valve problems
- HLHS: ↑ long-term survivors … unique needs and issues

Pediatric Cardiac Surgery Annual

Forty Years of The Fontan Operation: A Failed Strategy

Jack Rychik

Sem Thoracic Cardiovasc Surg 2010

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Fontan – not a cure …
So, where do we go next ??

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… from discovery to translation

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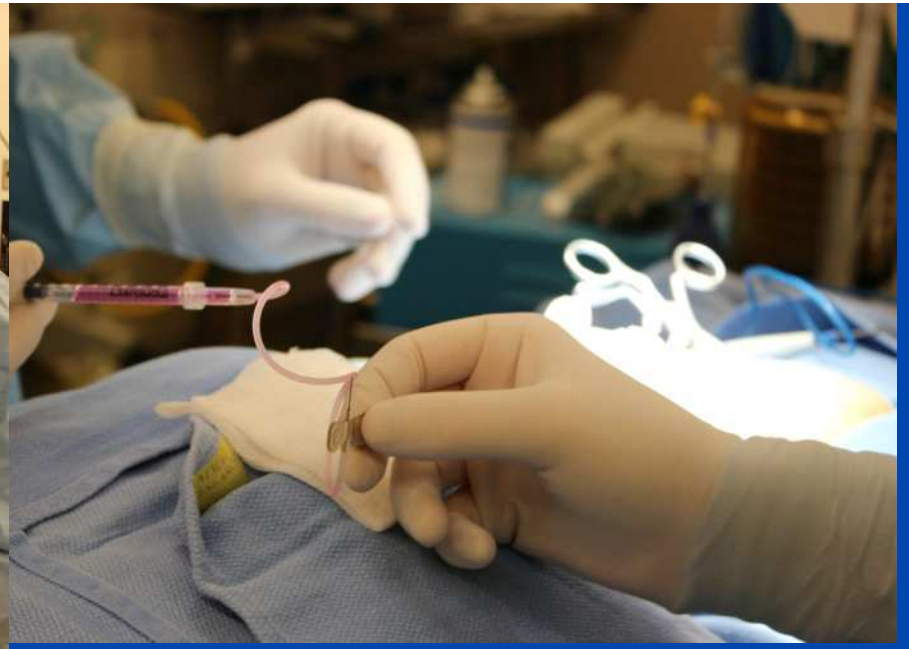

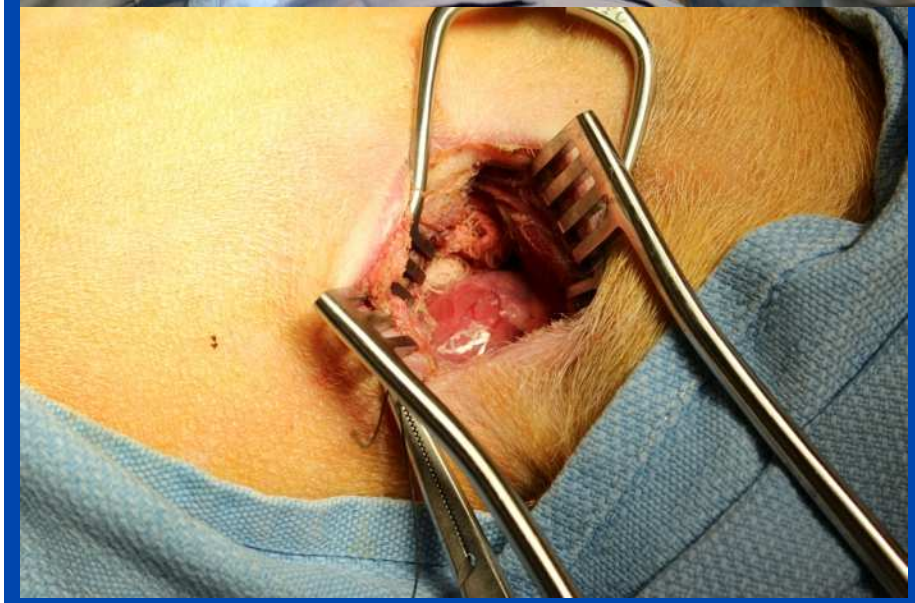

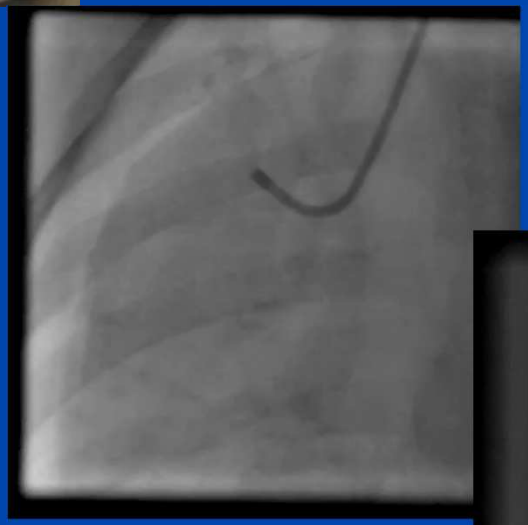

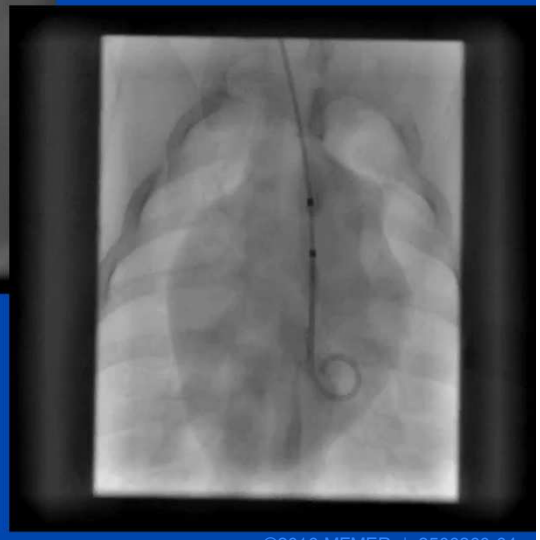

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Stem Cells for Single Ventricle Physiology: Current Clinical Phase 1 Trials

1. **HLHS:** (ClinicalTrials.gov: NCT01883076)
   - Direct intramyocardial injection
   - Umbilical cord blood derived stem cells
   - At the time of stage 2 surgery
   - HLHS patients (3 – 18 months)
2. **Failing Fontan:** (ClinicalTrials.gov: NCT02549625)
   - Intracoronary injection
   - Bone marrow derived mononuclear cells
   - RV morphology and failing Fontan, EF < 40% (2 – 30 yrs)

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