

MAYO CLINIC  
**FONTAN-ASSOCIATED LIVER DISEASE**  
 14th Challenges in Viral Hepatitis and Liver Disease  
 Lausanne, Switzerland, January 18, 2024

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 Mayo Clinic College of Medicine and Science  
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Division of  
 GASTROENTEROLOGY  
 & HEPATOLOGY

1

### Learning Objectives

- Understand the pathophysiology of Fontan associated liver disease (FALD).
- Describe approach to diagnosis and management
- Describe differential diagnosis of liver masses in FALD.
- Explain the role of cardiac and liver transplantation

2

### Case: Fontan and the Liver

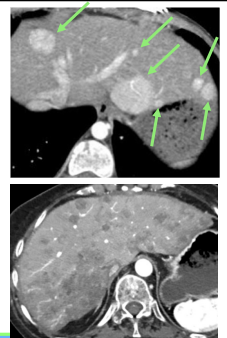
- 28-year-old female, Fontan procedure at age of 2 with multiple subsequent revisions is referred for MRI/MRE findings of multiple liver masses, many of which show delayed washout. Liver stiffness on MRE is 7.4 kPa which is in the cirrhosis range. MELD score is 8 and platelet count 140,000 with AFP 3.2 ng/mL.

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3

### Imaging

Arterial hyperenhancing hepatic nodules with delayed washout.



4

### Case: Fontan and the Liver

- 28 F, post Fontan, CTP-A, multiple hyperenhancing nodules and delayed washout. You would:
- A. Biopsy mass / masses
- B. List for combined heart and liver transplant
- C. List for liver transplant alone
- D. Atezolizumab plus bevacizumab
- E. Follow-up imaging in 3-6 months

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5

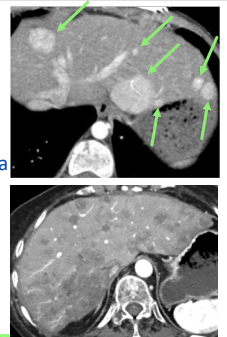
### Follow-Up

Hyperenhancing hepatic nodules

- Pathology: Focal Nodular Hyperplasia

- But patients are also at risk for hepatocellular carcinoma

Bryant, T., et al. Int J Cardiol. 2011. 151(3): p. 268-72.  
 Klessewetter, C.H., et al. Heart. 2007. 93(5): p. 579-84.  
 Wallihan, D.B., et al. Pediatr Radiol. 2013. 43(3): p. 330.  
 Asari, S.K., et al. N Engl J Med. 2013. 368(18): p. 1756-7.



6

### Fontan and the Liver: Questions

- Risks for liver disease post Fontan (FALD)
- How do you assess fibrosis/cirrhosis
- How do you diagnose HCC
- Indications for liver transplantation
- Combined heart and liver transplantation versus heart transplantation alone



7

### CONGENITAL HEART DISEASE SURGERY – Past



**Physiologist**

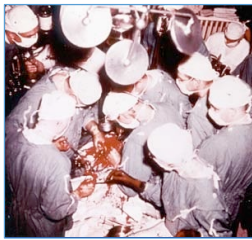
**John Gibbon**

**Lost his next  
two patients :  
stopped operating.**



8

### CONGENITAL HEART DISEASE SURGERY – Past



**Surgeon**

**C. Walton Lillehei**

**First cross  
circulation  
March 26, 1954.**



9

### CONGENITAL HEART DISEASE SURGERY – Past



**Surgeon**

**John W. Kirklin**

**Mechanical pump oxygenator  
for intracardiac repair  
in 1955.**

**Lost 4/8 cases**

**By 1956 : surgical mortality was 20%  
By 1957 : surgical mortality was 10%**



10

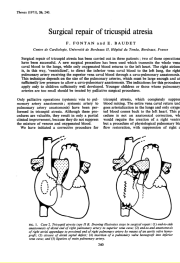
### CHD : SURGICAL COURAGE

- 1959 Senning: operation for d-TGA
- 1966 Ross: Repair of pulmonary atresia with aortic homograft
- 1968 Fontan operation for tricuspid atresia
- 1975 Jatene arterial switch for d-TGA
- 1978 Danielson: Ebstein repair

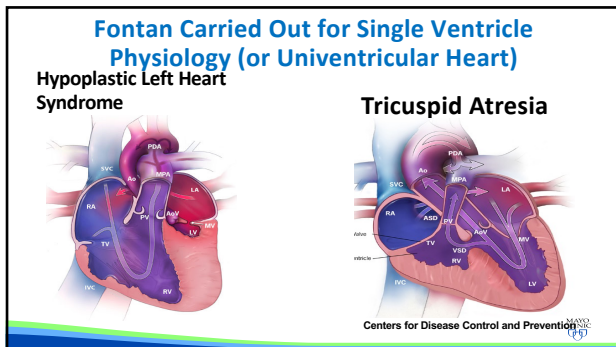


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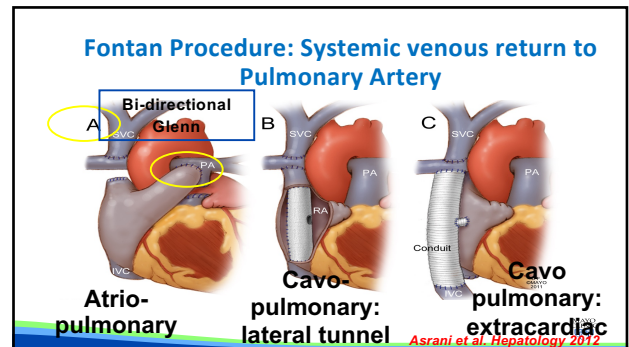
### Fontan Palliation



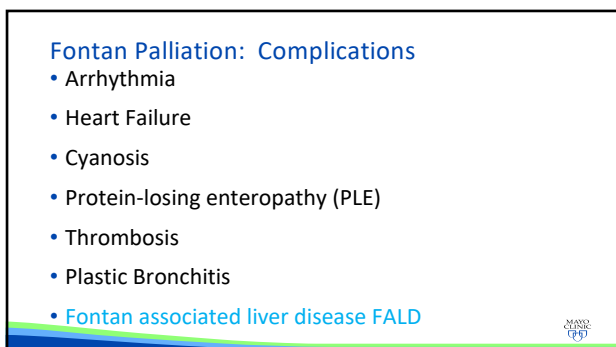
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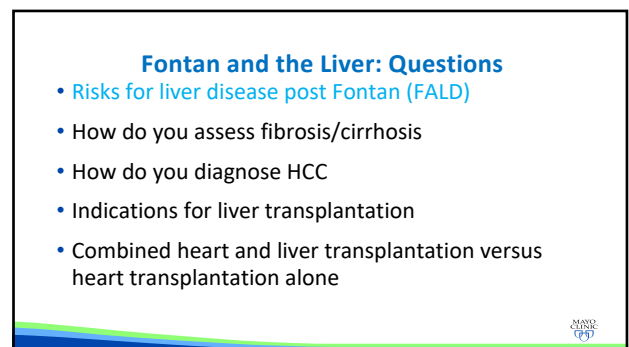
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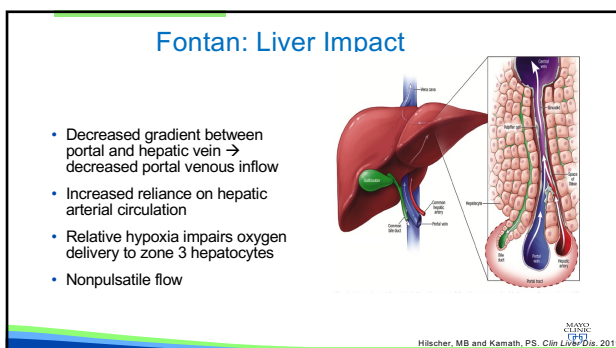
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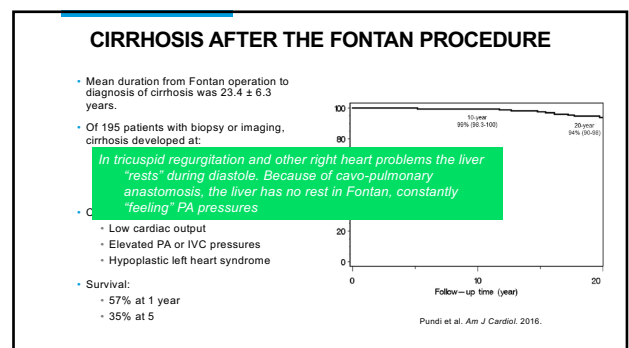
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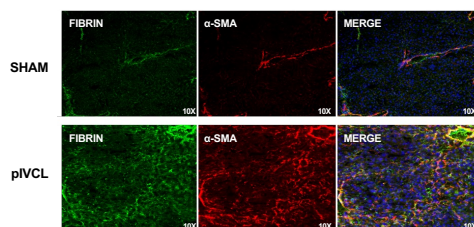
18

### CAN HEPATIC FIBROSIS BE PREVENTED?

- My colleagues, Drs Simonetto, Hilscher, and Vijay Shah have created what is arguably the first animal model of cardiac cirrhosis

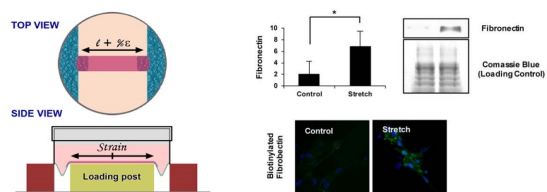
19

### Chronic hepatic congestion is associated with increased intrahepatic thrombosis



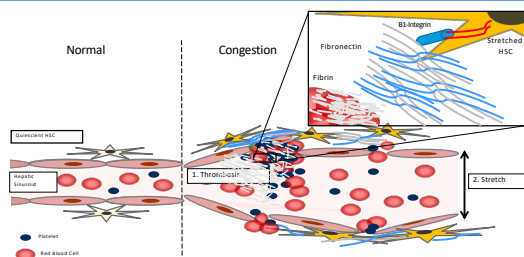
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### EXPOSURE OF HEPATIC STELLATE CELLS TO CYCLIC STRETCH ENHANCES FORMATION OF PROVISIONAL EXTRACELLULAR MATRIX

Simonetto DA, Hilscher MB et al. *Hepatology*, 2015

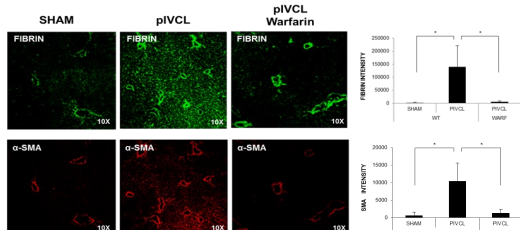
21

### Hepatic Congestion, Thrombosis, and Stretch Contribute to Congestive Hepatopathy and Fibrosis

Simonetto DA, Hilscher MB et al. *Hepatology*, 2015

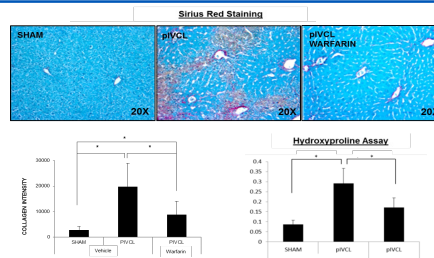
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### Warfarin treatment inhibits hepatic stellate cell activation and intravascular thrombosis after pIVCL

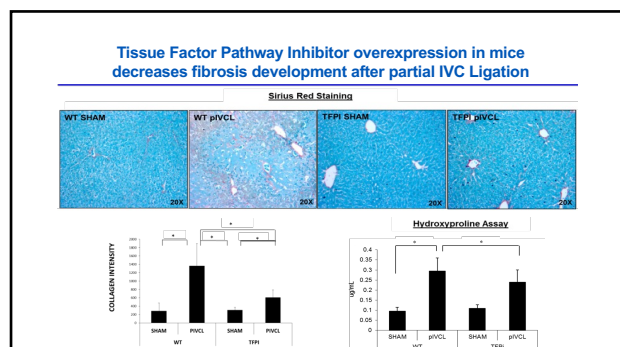


23

### Warfarin treatment inhibits fibrogenesis in liver congestion



24



25

**Summary of Lab Data**

1. Characterization of murine model of hepatic venous
2. **Can anticoagulation prevent hepatic fibrosis post-Fontan?**
3. thrombosis
4. Fibrosis secondary to chronic congestion is at least partially dependent on intravascular thrombosis

26

**CLINICAL PRESENTATION OF FALD**

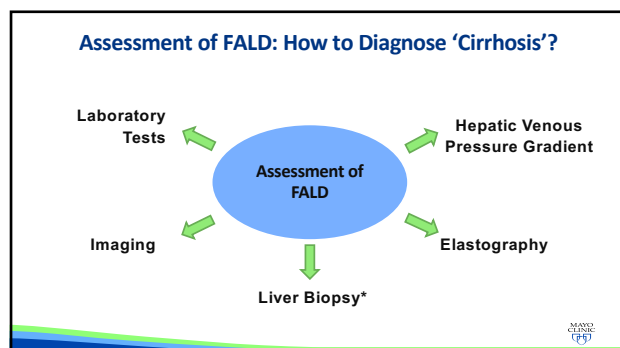
- Often asymptomatic
- Hepatic congestion → ascites, hepatomegaly, jaundice
- Laboratory abnormalities:
  - Predominantly indirect hyperbilirubinemia
  - Mild aminotransferase elevation
  - Moderate elevations in alkaline phosphatase and GGT
  - Prolonged PT
  - Decreased serum albumin

27

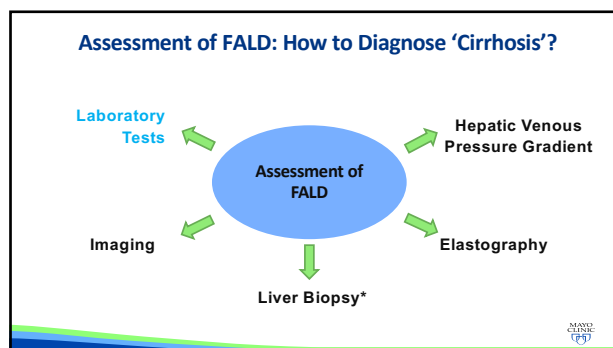
**Fontan and the Liver: Questions**

- Risks for liver disease post Fontan (FALD)
- How do you assess fibrosis/cirrhosis
- How do you diagnose HCC
- Indications for liver transplantation
- Combined heart and liver transplantation versus heart transplantation alone

28



29



30

### Assessment of FALD: Laboratory Tests

**May Not  
be Helpful**

Gamma-glutamyl transferase (GGT) – Always elevated  
Liver aminotransferases – Mild elevations  
Hyperbilirubinemia – Mostly mild and indirect  
Model of End-Stage Liver Disease: Renal dysfunction, anticoagulation



31

### Assessment of FALD: Laboratory Tests

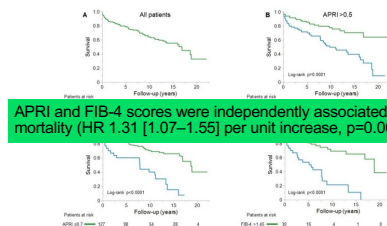
	Mild fibrosis (n = 16)*		Severe fibrosis (n = 22)*		P-value
	Median (IQR)	n (%) abnormal	Median (IQR)	n (%) abnormal	
ALT (IU/L)	28 (24–33)	1/15 (7%)	28 (23–37)	3/22 (14%)	0.915
AST (IU/L)	28 (23–33)	1/15 (7%)	28 (25–35)	5/22 (23%)	0.551
ALP (IU/L)	70 (54–97)	2/15 (13%)	81 (70–96)	2/22 (9%)	0.105
GGT (IU/L)	58 (46–104)	12/15 (80%)	42 (49–121)	19/22 (86%)	0.636
Bilirubin (mmol/L)	13 (11–19)	3/15 (20%)	16 (11–22)	9/22 (41%)	0.761
Albumin (g/L)	41 (40–43)	0/15	42 (40–44)	0/21	0.529
MELD-XI score	9.44 (9.44–10.98)	1/12 (8%)	9.44 (9.44–11.08)	3/22 (14%)	0.873

Munsterman ID et al. Eur Heart J. 2019 Apr 1;40(13)



32

### Lab-based scoring systems

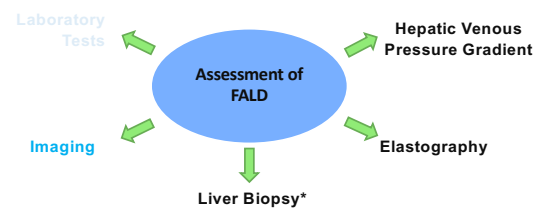


APRI and FIB-4 scores were independently associated with overall mortality (HR 1.31 [1.07–1.55] per unit increase, p=0.003; HR 2.15

Martin de Miguel I, et al. Heart 2023

33

### Assessment of FALD: How to Diagnose Cirrhosis?



34

### Fontan Associated Liver Disease (FALD): Diagnostic Difficulties

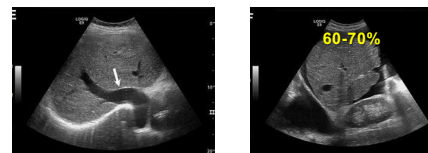
- Nodular pattern of liver in absence of cirrhosis
- Hypervascular nodules seen that are not HCC
- Focal Nodular Hyperplasia common



35

### Assessment of FALD: Imaging

#### Ultrasound

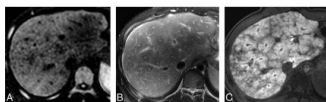


Bae JM et al. Eur J Radiol. 2018 Apr;85(4):850–6  
Wells et al. Abdom Radiol (NY). 2018 Aug;43(8):2037–2051.



36

## Imaging in FALD: CT and MRI



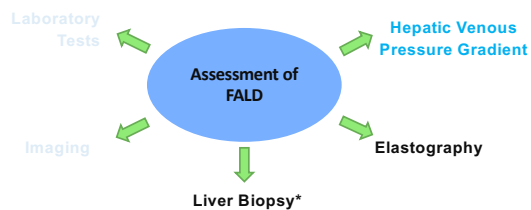
Radiologists often overcall Cirrhosis : Liver is typically nodular.  
Cannot reliably diagnose cirrhosis on imaging?

Brown MJ, Hilscher MB, Wells ML, et al. J Comput Assist Tomogr. 2023 Aug 11.



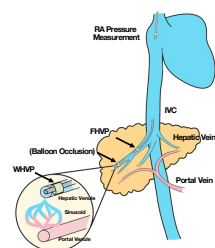
37

## Assessment of FALD: How to Diagnose Cirrhosis?



38

## Assessment of FALD: HVP



HVPG =  $\uparrow$ WHVP  $\uparrow$ FHVP

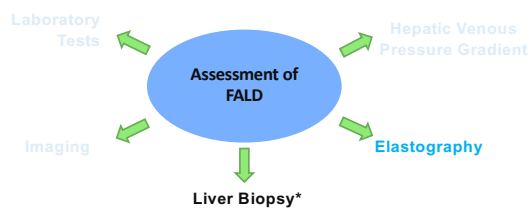
Mean HVPG =  $1.4 \pm 0.3$  mmHg

Egbe A et al. CJC Open. 2020 May 4;2(5):360-364.



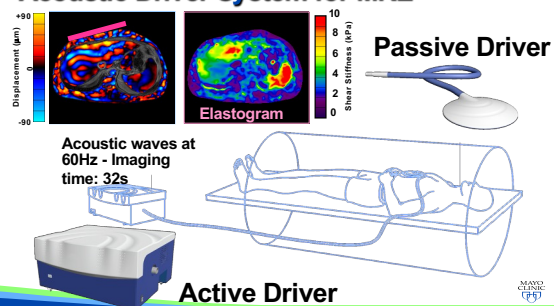
39

## Assessment of FALD: How to Diagnose Cirrhosis?



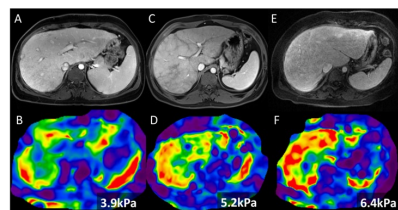
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## Acoustic Driver System for MRE



41

## Congestion increases liver stiffness on elastography



Hilscher MB, et al. Hepatology. 2023

42

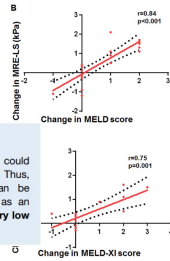
## Elastography in FALD

- In FALD, MRE correlates best with IVC pressure and Fontan pressures, not fibrosis.

Annals of  
stiffness  
assoc  
prog  
dise  
and

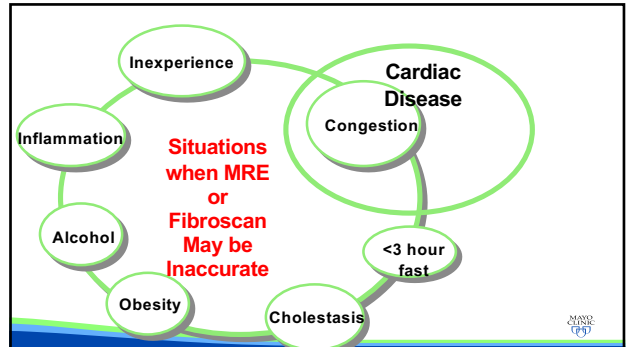
### Recommendations

- Longitudinal assessment of LSM during follow-up could help monitor patients and predict clinical outcomes. Thus, in surveillance programmes for FALD, LSM can be considered and easily performed when available as an adjunct to a liver ultrasound or MR examination (**Very low LoE, weak recommendation**).



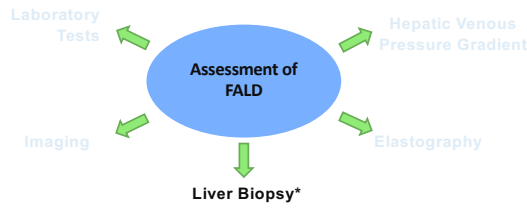
Tellez L, et al. J Hepatol. 2023 May 1;76(5):1289-304. Egbe A et al. Int J Cardiol. 2018 May 1;228:299-304.

43



44

## Assessment of FALD: How to Diagnose Cirrhosis?



45

## Assessment of FALD: Should Biopsy be the Gold-Standard?

Patient number	Biopsy type	Simultaneous dilation	Fibrosis	Bridging fibrosis	Regenerative nodules	Stage	Follow-up	Cause of death	Prolonged liver failure
1	TBL	Yes	Yes	No	No	I	Died: 69 months	Allograft vasculopathy	No
2	TBL	Yes	No	No	No	0	Alive: 137 months	NA	No
3	TBL	Yes	Yes	Yes	No	Died: 75 months	Allograft failure	Allograft vasculopathy	No
4	TBL	Yes	Yes	Yes	Yes	Died: 77 months	Allograft vasculopathy	Allograft vasculopathy	No
5	Unk.	Yes	Yes	Yes	Yes	Alive: 44 months	NA	NA	No
6	TBL	Yes	Yes	Yes	Yes	Died: 4 months	NA	Liver failure	Yes
7	TBL	Yes	Yes	Yes	No	Alive: 60 months	NA	NA	No
8	TBL	Yes	Yes	Yes	No	Died: PCD 479	NA	Enterobacter pneumonia	No
9	TBL	Yes	Yes	No	No	I	Alive: 50 months	NA	No
10	TBL	Yes	Yes	No	No	I	Alive: 46 months	NA	No
11	TBL	Yes	Yes	No	No	I	Alive: 46 months	NA	No
12	TBL	Yes	Yes	Yes	No	II	Alive: 47 months	NA	No
13	TBL	Yes	Yes	Yes	No	II	Alive: 46 months	NA	No
14	TBL	Yes	Yes	Yes	Yes	II	Alive: 43 months	NA	No
15	TBL	Yes	Yes	Yes	Yes	II	Alive: 27 months	NA	No
16	TBL	No	No	No	No	Died: PCD 35	NA	Dilated aortic valve disease	No
17	TBL	Yes	Yes	No	No	II	Alive: 26 months	NA	No
18	TBL	Yes	Yes	Yes	No	Died: PCD 13	NA	Aspergillus pneumonia	No
19	TBL	Yes	Yes	Yes	No	II	Alive: 42 months	NA	No
20	TBL	Yes	Yes	Yes	No	Died: 10 months	NA	Liver failure	Yes
21	TBL	Yes	Yes	Yes	Yes	Died: 3 months	NA	Sepsis	Yes

46

## Role of liver biopsy in determining need for CHLT – Penn experience

- Pre-operative liver biopsy pathology graded on fibrosis
  - Based on Standard Metavir fibrosis score (F0-F4)
    - F0: No fibrosis
    - F1: Mild fibrosis (portal fibrosis without septa)

		Biopsy		Explant		Total		Concordance			
	N	Median fibrosis score				#	%	#	%	#	%
Heart alone	25	2				1	4%	1	4%	2	8%
Heart + liver	21	3				1	5%	1	5%	5	24%

Higher degree of fibrosis may be associated with worse prognosis, but biopsy can be misleading- often less fibrosis than explant

47

## When Do I Suspect the Patient Has Cirrhosis?

### 1. Patient with congenital heart disease and:

- Variceal bleeding
- Ascites – SBP
- Hepatic encephalopathy

### 2. Physical examination:

- Splenomegaly
- Spider nevi
- Palmar erythema

48



### When Do You Suspect the Patient Has Cardiac Cirrhosis? (cont.)

3. **Labs:**
  - a. Thrombocytopenia (often, first laboratory abnormality)
  - b. AST > ALT
  - c. Low albumin or elevated INR (caution: also seen in PLE)
4. **Abdominal imaging:**
  - a. Porto-systemic collaterals
  - b. Splenomegaly
5. **Endoscopy:**
  - a. Varices



49

### Approach to Diagnosing Cirrhosis

- Clinical examination
- Baseline CBC and liver biochemical tests
- If clinical fibrosis is suspected, **Heart transplant Surgeons want Biopsy!** Hepatic biopsy required.
- Please do NOT make a diagnosis of cirrhosis unless you have at least two lines of supporting evidence to justify diagnosis.



50

### FALD: Diagnosis of Cirrhosis – Practical Issues

I am worried only if patients have complications of portal hypertension or HCC.

Hepatic fibrosis is invariable at 10 years (Goldberg DJ et al J Am Heart Assoc. 2017 Apr 26;6(5): pii: e004809)

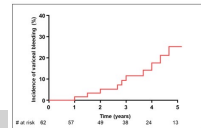
Thrombocytopenia may be more meaningful in diagnosis of cirrhosis than MR elastography

APRI and FIB-4 may correlate with FALD mortality



51

### Varices in FALD



	Prevalence of varices	Annual incidence of new varices	Variceal hemorrhage
FALD	34%	9%/year	5%/year
Compensated cirrhosis	30-40%	7-8%/year	10-15%/year
Decompensated cirrhosis	85%	22% at 1 year 51% at 3 years	10-15%/year

Goldberg DJ, et al. Hepatology. 2018; Egbe A, et al. Under review. 2018

52

### Fontan and the Liver: Questions

- Risks for liver disease post Fontan (FALD)
- How do you assess fibrosis/cirrhosis
- How do you diagnose HCC
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- Combined heart and liver transplantation versus heart transplantation alone



53

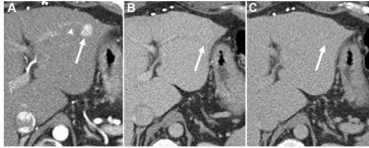
### Liver Masses in FALD

- Benign hyperenhancing masses in Fontan patients may demonstrate delayed washout and be mistaken for HCC by imaging criteria.
- HCC: Portal phase washout, mosaic architecture, elevated AFP
- Wells ML et al Abdom Radiol (NY). 2017;42(11):2623-2631



54

### Typical FNH in FALD: Most Common Arterial Enhancing Mass

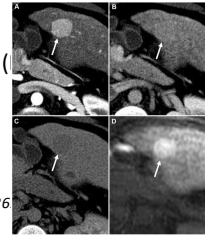


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55

### FNH Showing Features of HCC: Arterial enhancement and Delayed Washout

- FNH on biopsy
- No growth over 24 months (



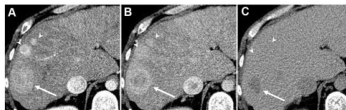
- *Abdom Radiol (NY)*, 2017 Nov;42(11):26

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56

### HCC in FALD: Characteristics

- Atypical/heterogenous portal phase washout with HCC



**Imaging features associated with HCC:**  
Venous invasion OR  
Portal venous washout, threshold growth,  
mosaic architecture (and elevated AFP)

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57

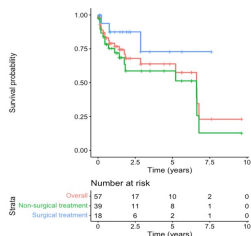
### HCC IN FALD

- Neither age at Fontan nor time since Fontan operation correlated with HCC.
- Approximately half were asymptomatic.
- One-quarter had normal AFP levels.
- Approximately half occurred in patients with MELD-XI scores <11, APRI scores <0.05, and FIB-4 scores <1.45

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58

### OUTCOMES OF FONTAN PATIENTS WITH HCC

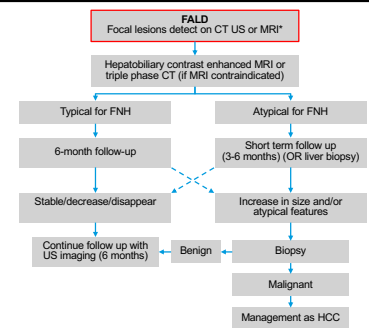


- Surgical therapy with intent to cure in 18/38:
  - 9 underwent CHLT (0 recurrence)
  - 9 underwent surgical resection (recurrence in 44%)
- 33 underwent liver-directed therapy
  - 15/33 had evidence of viable tumor on follow up imaging
- 3 underwent systemic therapy
- 9 received no active cancer treatment
- Median follow up of 1.45 years:
  - 64% survival
  - 1-year survival rate of 81%

Kim Y, Hotell M, Hilscher M, et al. Under review

59

### EVALUATION OF FOCAL LIVER LESIONS: FALD



\*Elevation of AFP favors malignancy in any situation

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60

### Fontan and the Liver: Questions

- Risks for liver disease post Fontan (FALD)
- How do you assess fibrosis/cirrhosis
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- Combined heart and liver transplantation versus heart transplantation alone



61

### Fontan Associated Liver Disease: Indications for Liver Transplantation

- Complications of portal hypertension/liver failure
- Hepatocellular carcinoma



62

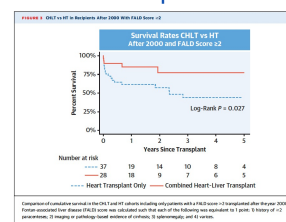
### Fontan and the Liver: Questions

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63

### Combined heart-liver transplantation versus isolated heart transplantation in FALD



64

### Is the Liver Good for the Heart?

American Journal of Transplantation 2016; XX: 1-10  
Wiley Periodicals Inc.

© Copyright 2016 The American Society of Transplantation  
and the American Society of Transplant Surgeons  
doi: 10.1111/ajt.13870

#### Liver Allograft Provides Immunoprotection for the Cardiac Allograft in Combined Heart-Liver Transplantation

T. W. Wong<sup>1</sup>, M. J. Gandhi<sup>2</sup>, R. C. Daly<sup>1</sup>,  
S. S. Kushnaha<sup>3</sup>, N. L. Pereira<sup>1</sup>, C. B. Rosen<sup>1</sup>,  
M. D. Stegall<sup>1</sup>, J. K. Heimbach<sup>1</sup> and T. Taner<sup>1,\*</sup>

vasculopathy; CNL, calcineurin inhibitor; DSA, donor-specific HLA antibody; ECMO, extracorporeal membrane oxygenation; IHT, isolated heart transplantation; ISHLT, International Society for Heart and Lung Transplantation; RRT, renal replacement therapy.



65

### Rejection: SLH < IHT

TCMR, n (%)	SLH	IHT	P
	7 (31.8)	189 (84.8)	<0.0001

A total of 7 patients (age  $43 \pm 7$  years, 86% women) with high allosensitization (median calculated panel reactive antibody = 77%) underwent HALT (heart after liver transplant). All had significant, unacceptable donor specific antibodies (DSA) (>4,000 mean fluorescence antibody). Prospective pre-operative flow cytometric T-cell crossmatch was positive in all, and B-cell crossmatch was positive in 5 of 7. After HALT, retrospective crossmatch (B- and T-cell) became negative in all. J Am Coll Cardiol. 2021;77:1331



66

### Fontan Associated Liver Disease: Indications for Combined Heart and Liver Transplantation

- Liver transplant: for complications of portal hypertension/Hepatocellular carcinoma
- *If there is an indication for liver transplantation, procedure should always be accompanied by cardiac transplantation*
- Highly sensitized candidates for heart transplant: lean towards combined procedure
- *Cirrhosis without complications and excellent liver function is not necessarily an indication for combined liver - heart transplantation*



67

### Fontan Associated Liver Disease: Take Home Messages

- Hepatic fibrosis invariable after 10 years; cirrhosis 40% at 30 years
- Biopsy probably *not* gold standard for diagnosis of cirrhosis given patchy distribution of hepatic fibrosis
- HVPG, MRE, LSM threshold for development of complications unknown. HVPG not useful measure to determine complication risk.
- Development of HCC in absence of traditional standards for diagnosis of cirrhosis. Annual liver imaging > 10 years post Fontan
- Criteria for determining need for combined heart-liver transplant versus heart transplant alone need to be developed.



68