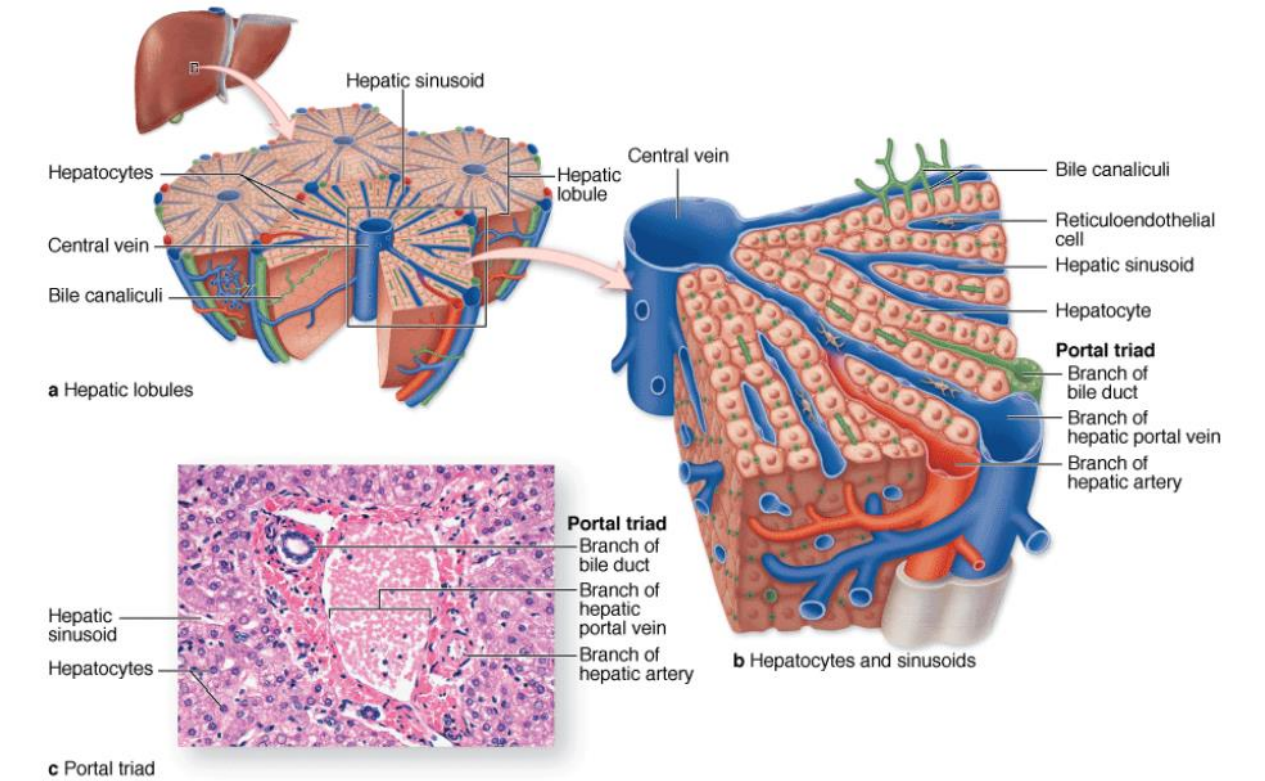
"Liver disease in single ventricle patients - have we learned anything?"

Professor Winita Hardikar
Head, Liver and Intestinal Transplantation
Director Department of Gastroenterology and Clinical Nutrition
Royal Children's Hospital Melbourne

Outline

- Summarize the current knowledge of hepatic complications of the Fontan circulation
- Identification of liver complications
- Ongoing monitoring-which investigations?

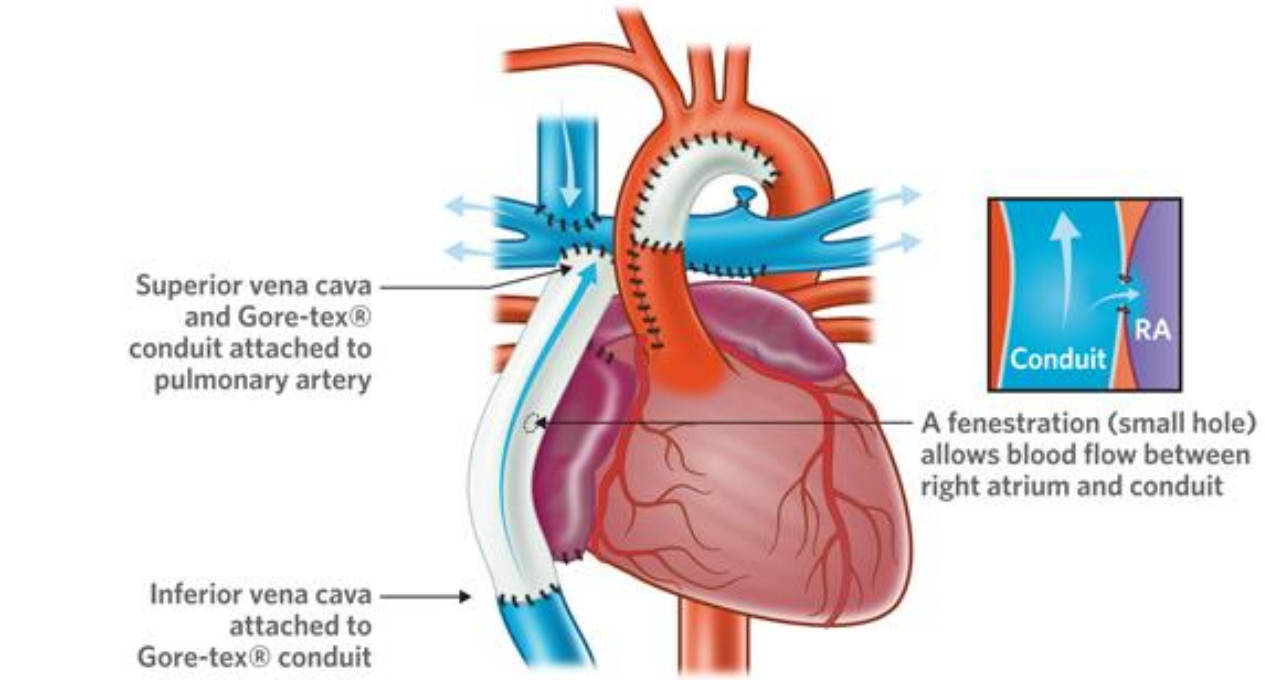
Normal liver structure



- Complex 3D structure of hepatic lobules
- Unique
- Blood supply 70% portal vein, 20% hepatic artery (mainly bile ducts)
- Cells along the triad have differing functions

RISKY POSITION Between 2 venous circulations- splanchnic and pulmonary *

Fontan circulation:
The cardiology/cardiac surgery view



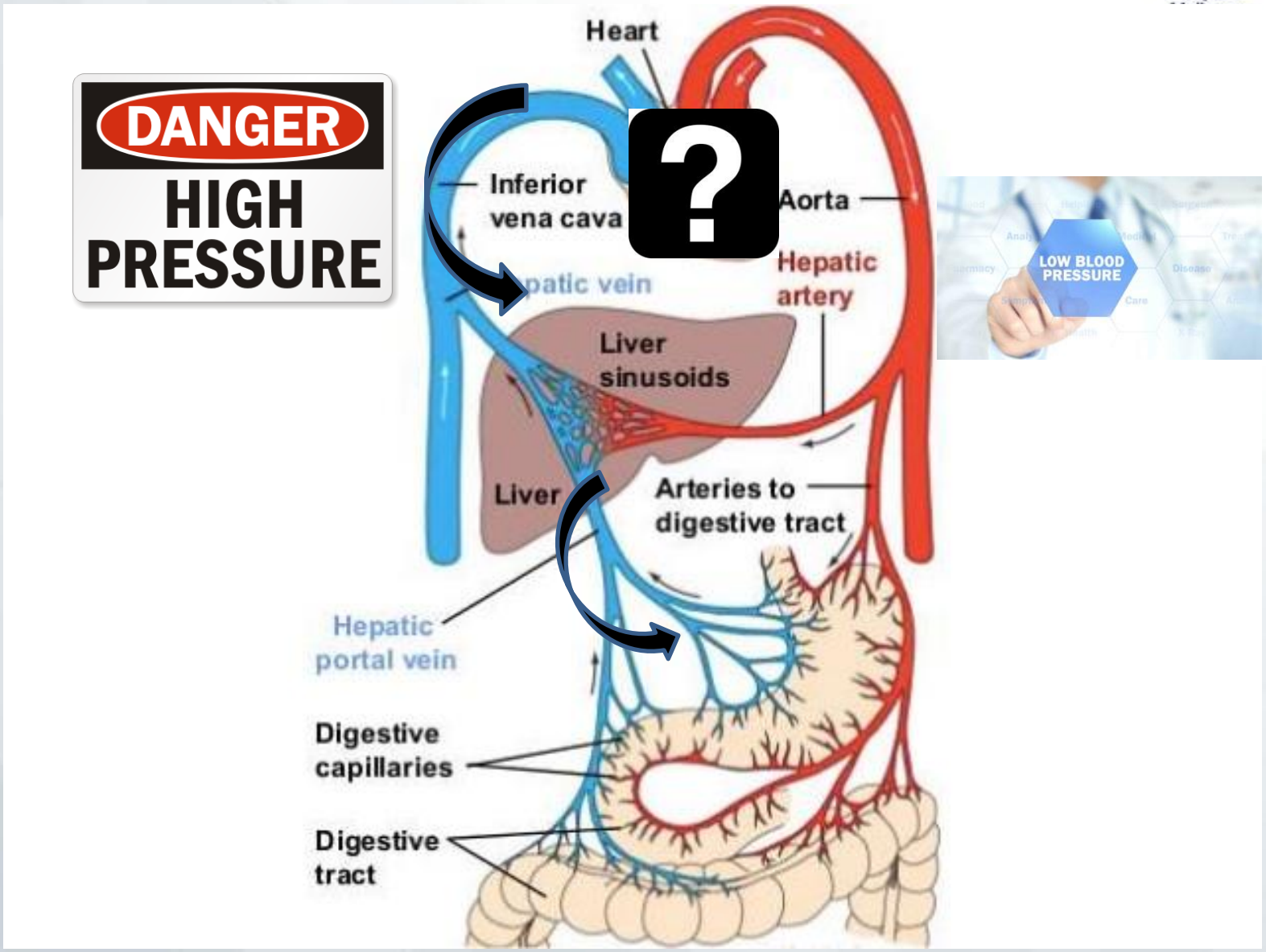
Problems fixed:
1. Death
2. normalization of systemic oxygen saturation
3. normalization of ventricular volume load

BUT….

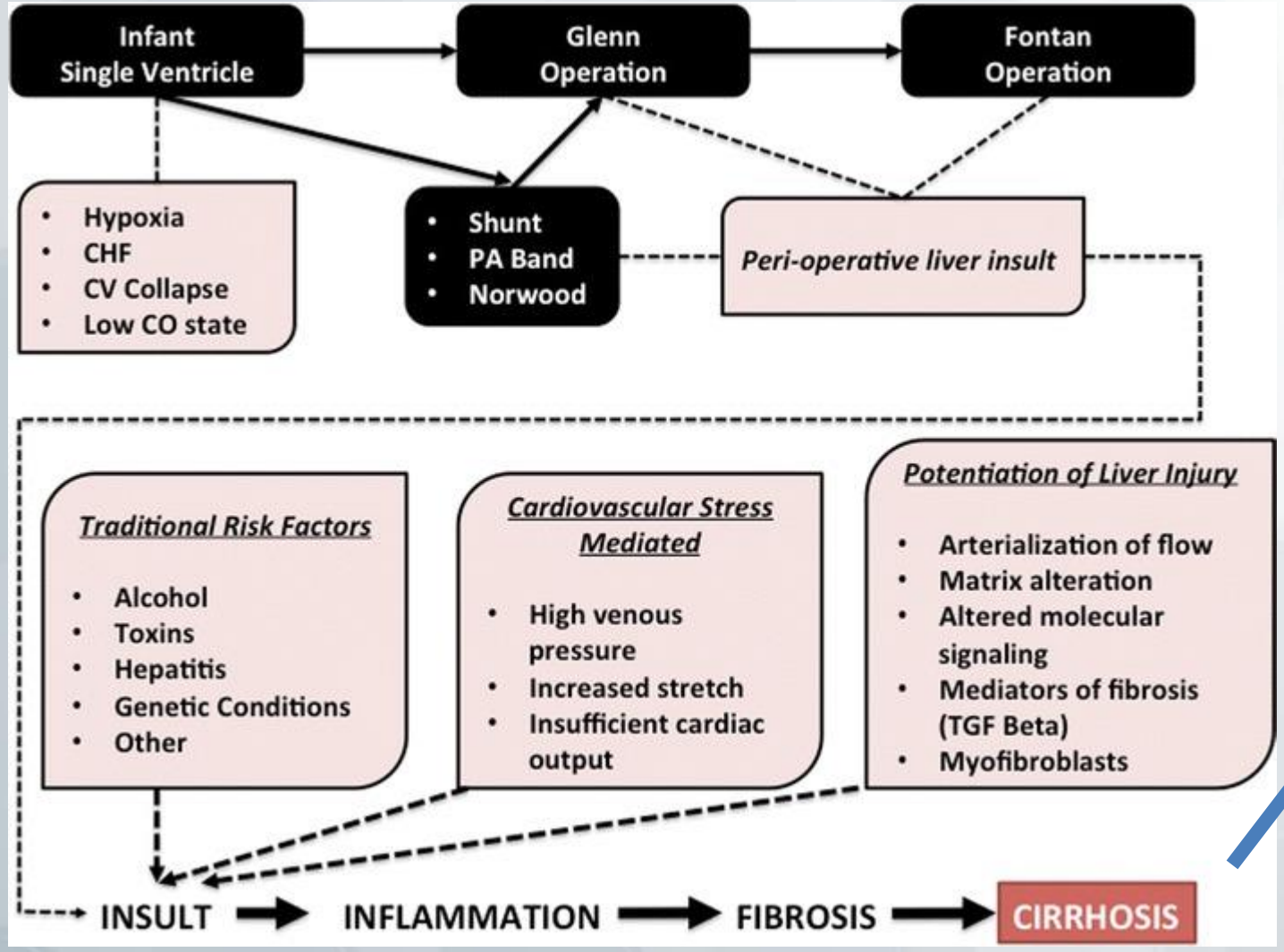
Fontan circulation:The hepatologists view

- Chronically elevated right atrial pressure causing repetitive mechanical stretch and compression (passive congestion)

- tissue hypoxia (low cardiac output)

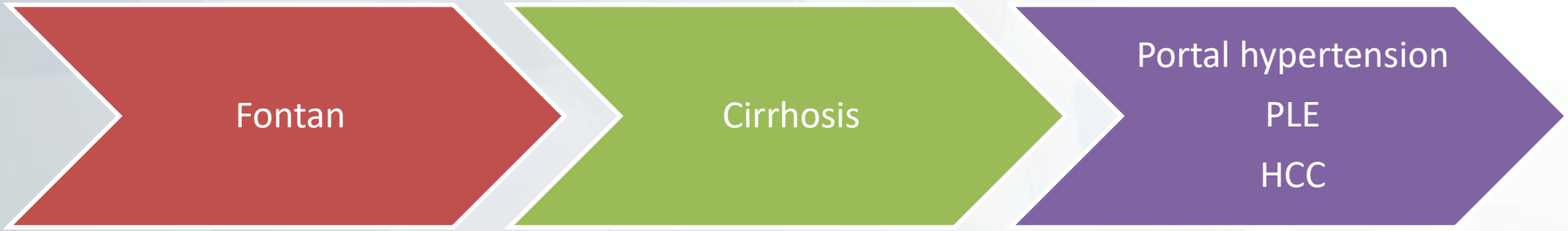


Proposed mechanisms of liver injury



PLE
Portal hypertension
HCC

Rychik J et al *Pediatric Cardiology*. 2012;33(7):1001-2



So how common are these complications?

Liver complications of long term Fontan circulation: **Fibrosis/ Cirrhosis**

Liver biopsy study

- n= 67 patients, mean age 17.3 yrs, mean time from Fontan 14.9 yrs
- Quantitative determination of hepatic fibrosis using Sirius red staining (%CD collagen deposition)
- Median 21.6% (8.7%-49.4%) vs 2.6% (2.2%-3.0%) in controls
- significant correlation between time from Fontan and degree of Sirius red staining ($r=0.33$, $P<0.01$)
- No correlation with %CD: liver enzymes, platelet count, median IVC pressure(13 mm Hg), ventricular morphology or severity of AV valve insufficiency.

Multicenter cross sectional study

- n=241,median time since Fontan 20.3 years [5.4-34.5]
- hepatic imaging (n = 54) and liver histology (n = 68)
- Up to 1/3 had cirrhosis

1. *Goldberg et al J Am Heart Assoc. 2017*
2. *Wu et al J Thoracic and Cardiovascular Surgery 2017:153;656-664*

Liver complications of long term Fontan circulation: Portal hypertension/PLE

Portal hypertension

- n=73 post-Fontan patients (mean age 24±11 years, mean interval from Fontan 17±6 years)
- VAST score: 1 point each for Varices, Ascites, Splenomegaly or Thrombocytopenia
- portal hypertension (VAST score ≥2) in 26 **(36%)**
- 19 major adverse events: death (n=12), transplant (n=6), and HCC (n=1).
- A significant relationship between VAST score ≥2 and major adverse events (OR=9.8, 95% CI [2.9-32.7]). After adjusting for time since Fontan, SLV, age, hemoglobin and type of failure, VAST score ≥2 remained significant (OR=9.1, 95% CI [1.4-57.6]).
- Fontan patients with portal hypertension have a 9-fold increased risk for a major adverse event

Protein losing enteropathy- occurs in 10-15%

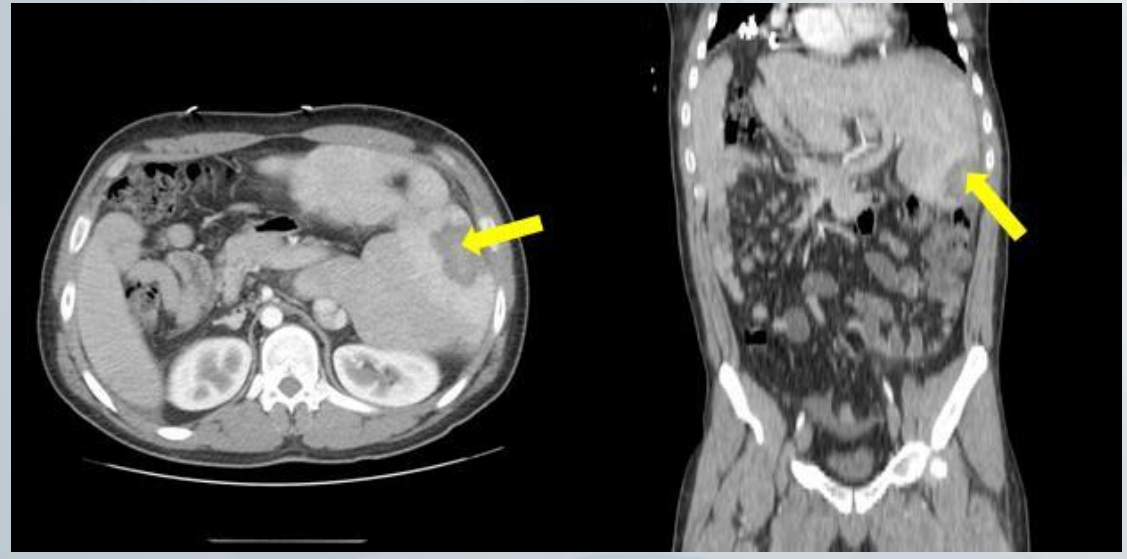
Varices- 9-38%, bleeding rare

Hepatic encephalopathy- rare

Elder RW et al Int J Cardiol. 2013 Oct 9;168(4):3764-9, Feldt J Cardiovas surg 1996

Liver complications of long term Fontan circulation: **Hepatocellular cancer**

- Estimated incidence:1.5-5% per year, many case reports and small series
- Usually in setting of cirrhosis
- Also seen as rare complication of hepatic venous congestions eg Budd Chiari, Constrictive pericarditis



Asrani SK, Warnes CA, Kamath PS. Hepatocellular carcinoma after the Fontan procedure. N Engl J Med. 2013;368(18):1756-7.
P. Nguyen, N. Galvan, M. Kueht, C. O'Mahony, R. Cotton, A. Rana, J. Goss. ATC 2017: A87
HCC and Cardiac Cirrhosis After the Fontan Procedure in a Patient with Congenital Heart Disease and Situs Inversus.

Liver complications of long term Fontan circulation: **Hepatocellular cancer**

Online survey (REDCap) to 28/ 312 hepatologists and cardiologists

Results: Routine liver screening by 86%, using ultrasound (79%), AFP (75%), or CT or MRI imaging (29%). Screening performed biannually in 54%, annually in 38%, and based on findings in 8%. HCC reported in 25 Fontan patients at a median age of 28.5 (19-53) years, had HCC detected at a median post Fontan interval of 21 (10-35) years.

The most common presenting symptoms were ascites (28%), RUQ pain (24%), and hepatomegaly (24%).

Routine screening detected HCC in 9/25 patients; 8/9 of those screened cases were caught at early stage with single tumor.

Prior to diagnosis with HCC, the median interval since prior imaging was 12 (1-42) months.

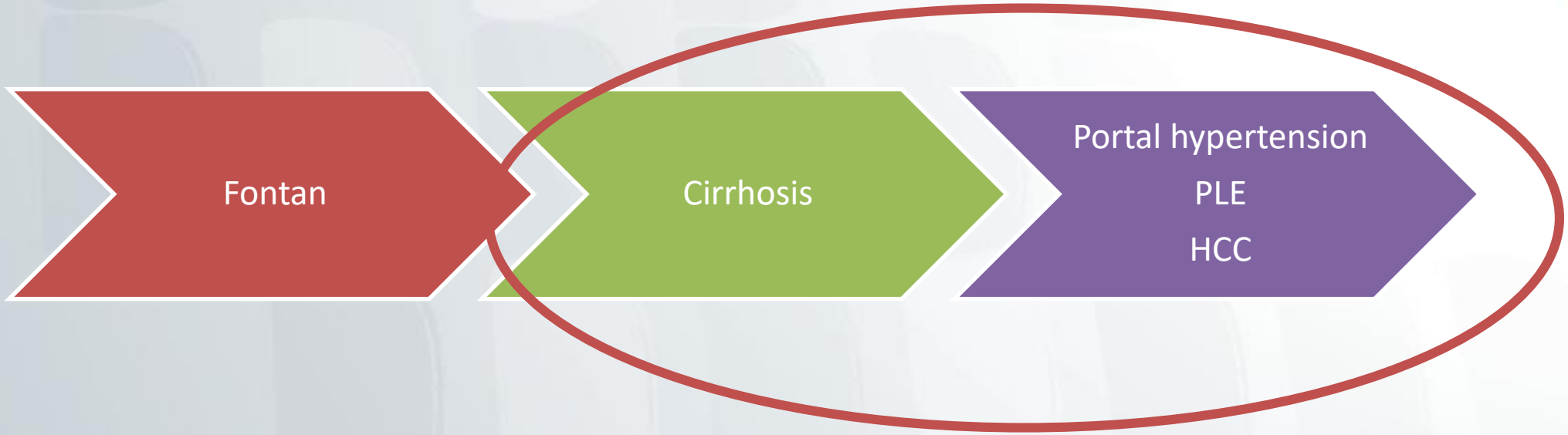
Patients without prior or recent (within 12 months) liver imaging more likely to present with multiple liver masses or metastatic disease (91%).

88% of patients deceased by 1 year after diagnosis had no prior or recent screening.

Conclusion: Patients with Fontan circulation at increased risk of HCC and should be screened according to guidelines.

Early diagnosis of HCC may allow for improved treatment strategies and prolonged survival.

Dickmeyer et al AASLD Nov 2015 presentation

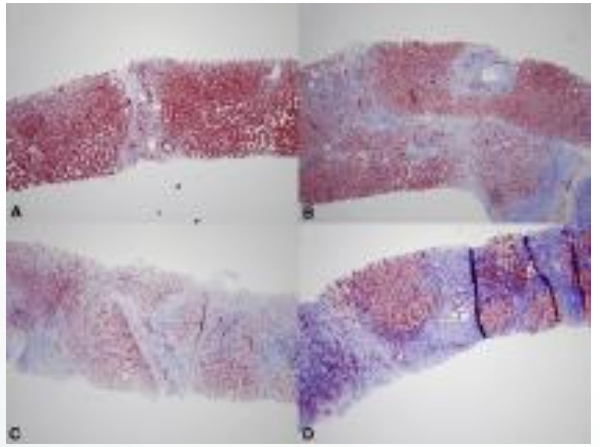


How do we identify and monitor for these complications?

Measuring and Monitoring for Fibrosis/Cirrhosis

Direct

- liver biopsy-gold standard BUT
  - Invasive
  - small sample size,
  - bleeding risk (venous congestion, anticoagulation)



Indirect

- **"Liver function tests"- in outpatients**
  - Elevation of GGT in 40-60%, ALT/AST 1/3, Bilirubin in 25-40% (mild and unconjugated)
  - Decreased TP and albumin in 5-10%
  - Prothrombin time (PT) is abnormal in 65-79% of older cohorts
    (related to deficiencies in liver-derived coagulation factors)
  - **Do not correlate with degree of liver injury**

Wu et al Liver health in adults with Fontan circulation: A multicenter cross-sectional study The Journal of Thoracic and Cardiovascular Surgery 2017:153;656-664

Indirect measures of Fibrosis/Cirrhosis: Imaging

Ultrasound

FINDINGS

- hepatic vein and suprahepatic IVC dilation
- Hepatomegaly
- Increased echogenicity
- nodular edge
- intra and extrahepatic veno-venous collaterals
- Splenomegaly
- Reversed portal vein flow
- Hypervascular nodules (arterialisation from low portal flow)
- Gastro-oesophageal varices

CONS

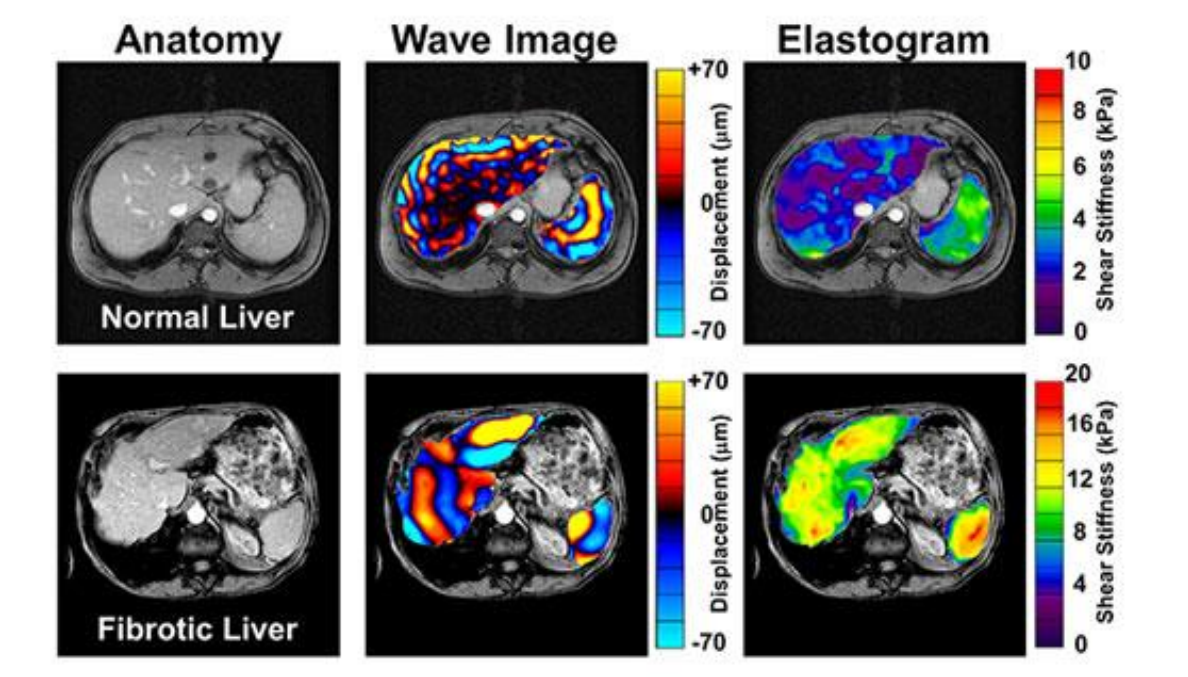
- Labour intensive/Availability/Cost
- Operator dependent
- Sensitivity-fibrosis?

CIRRHOSIS

TUMOURS

MRE

- Correlates with APRI, time from Fontan (n=50, 16% had liver biopsy)
- Overestimates in presence of venous congestion
- Can be done at time of cardiac MRI
- Needs further evaluation



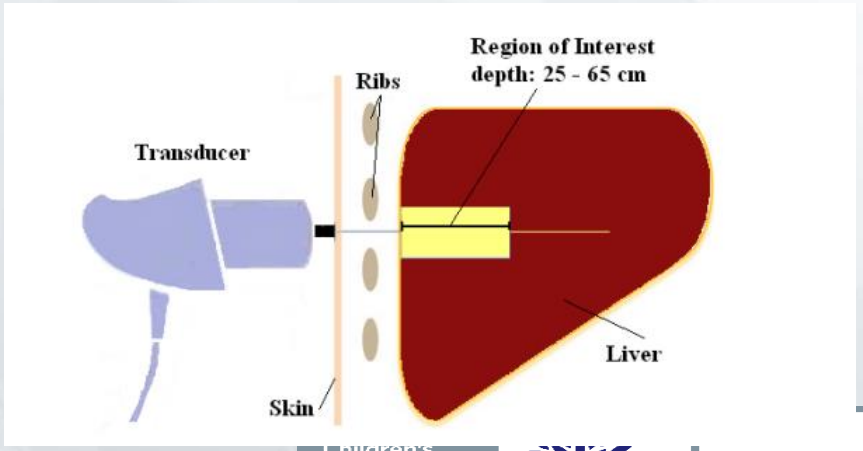
Indirect measures of Fibrosis/Cirrhosis: Serum fibrosis panels

Name of score	Parameters	Studied in Fontan	Useful?
Fibrotest	alfa 2 –macroglobulin, apolipoprotein A1, haptoglobin, GGT, bilirubin	Yes- small study, correlated with TE, no biopsy Yes n=152 (ANZ study), correlated with TE	Yes, will be-still need cut-off's
ELF(Enhanced Liver Fibrosis)	hyaluronic acid, aminoterminal peptide of type III collagen, Tissue inhibitor of matrix metalloproteinase		
APRI	AST/ULN/plt X 100	yes	no
Forns index	plt, GGT, age,cholesterol	n=204, 25% hepatic complications AUROC 0.78 (Baek)	yes
FIB-4 score	age x AST/ platelet count x ALT	yes	no
MELD-XI	MELD excluding INR	YES, correlates with fibrosis on biopsy	No cut off

Baek Heart 2010, Evans Pediatr Cardiol 2016, Lindsay Am J Cardiol 2015

Indirect measures of Fibrosis/Cirrhosis: Transient Elastography (Fibroscan™)

- Ultrasonic transducer mounted on the axis of a vibrator
- Vibration induces an elastic shear wave which propogates through tissue
- Pulse-echo ultrasound acqusition to follow shear wave and measure velocity
- Velocity proportional to stiffness of tissue (harder the tissue, faster propagation)
- Results as kilopascals



Indirect measures of Fibrosis/Cirrhosis: Transient Elastography (Fibroscan™)

Factors confounding TE measurement	Solution
Abnormal LFTs (especially ALT> 5 X ULN)	Avoid flares
Meal	requires fasting- 3-4 hours
Fat	XL probe and CAP (controlled attenuation parameter) measures ultrasound attenuation at the center frequency (expressed as dB/m) of the M probe
Disease process eg HBV, NASH	Validation in Fontan required- see studies
Venous congestion	Will need validation

LSM proportional to CVP

Landrace pigs

- studied the direct relationship between the CVP and LS measured by Fibroscan.
- **Clamping of the inferior caval vein increased LS from 3.1 to 27.8 kPa, reopening reversed LS within 5 min to almost normal values of 5.1 kPa**
- Isolated pig liver, studied using clamping the upper and lower caval, PV and HA
- Stepwise increase of intravenous pressure to 36 cm of water column (3.5 kPa) linearly and reversibly increased LS to the upper detection limit of 75 kPa

Humans

- n=10, decompensated congestive heart failure, LSM before and after recompensation
  - Initial LS elevated in all patients, in 8/10 level suggested liver cirrhosis (median 40.7 kPa)
  - Upon recompensation (median weight loss 3 kg), LS decreased in all 10 to median 17.8 kPa
  - Not due to inflammation as initial LFTs only slightly elevated and did not change significantly

Millonig, Gunda et al. Liver stiffness is directly influenced by central venous pressure Journal of Hepatology , Volume 52 , Issue 2 , 206 - 2010

Fibroscan in Fontan patients

- n=39, 11+/- 5.5 years, time since Fontan median 69 months (2-180 mths)
- TE compared to Fibrotest and Acti test (tool of necro-inflammatory activity)
- LSM correlated with age, time interval since Fontan, biochemical fibrosis score, necroinflammatory marker
- 87% had >F2 (METAVIR)

Friedrich-Rust M et al J Thorac Cardiovasc Surg 2008;135:560-567

ANZ Fontan registry study

- n= 152 Mean age 19.8 ± 9.3 yrs, mean time since Fontan 14.1 ± 7.6 yrs
- Features suggestive of hepatic **fibrosis on ultrasound** in 87/143(**61%**) , no HCC
- **Fibroscan** median kPa was ≥10 in 117/133(88%), ≥15 in 75/133(56%), and **≥20 in** 41/133(**31%**)
- FibroTest score ≥0.49 (equivalent to ≥F2 fibrosis) in 54/118, (46%)
- **FibroTest score correlated with FibroScan** value (r=0.24,p=0.015)
- **Ultrasound features of hepatic fibrosis associated with a higher Fibroscan** median kPa (19.5 vs 15.4, p=0.002).

Wilson et al AHA Nov 2106 (under review)

Measuring and Monitoring for Hepatocellular cancer

- Screening required in many chronic liver diseases but ideal method and frequency uncertain
- Ultrasound – mass, particularly in a cirrhotic liver
- Characteristic features on triple phase CT with peripheral IV contrast
  - Hepatic arterial phase 30-45s- enhancement of HCC before rest of liver
  - Portal venous phase 75-90s- normal liver enhancement, HCC not seen "early washout"** **diagnostic of HCC** (superior to histology)
  - Delayed phase >5 mins- normal liver washes out
  - But features maybe altered by high SVP and low cardiac output
  - Note hypervascular nodules aterial enhancing but benign FNH
- MRI can also be used (but issues if pacemaker)
- AFP>200ng/mL diagnostic, rising value is of significance, elevated in % of HCC
- Liver biopsy: risk of seeding, maybe difficult to differentiate

Monitoring of Fontan Patients: Conclusion

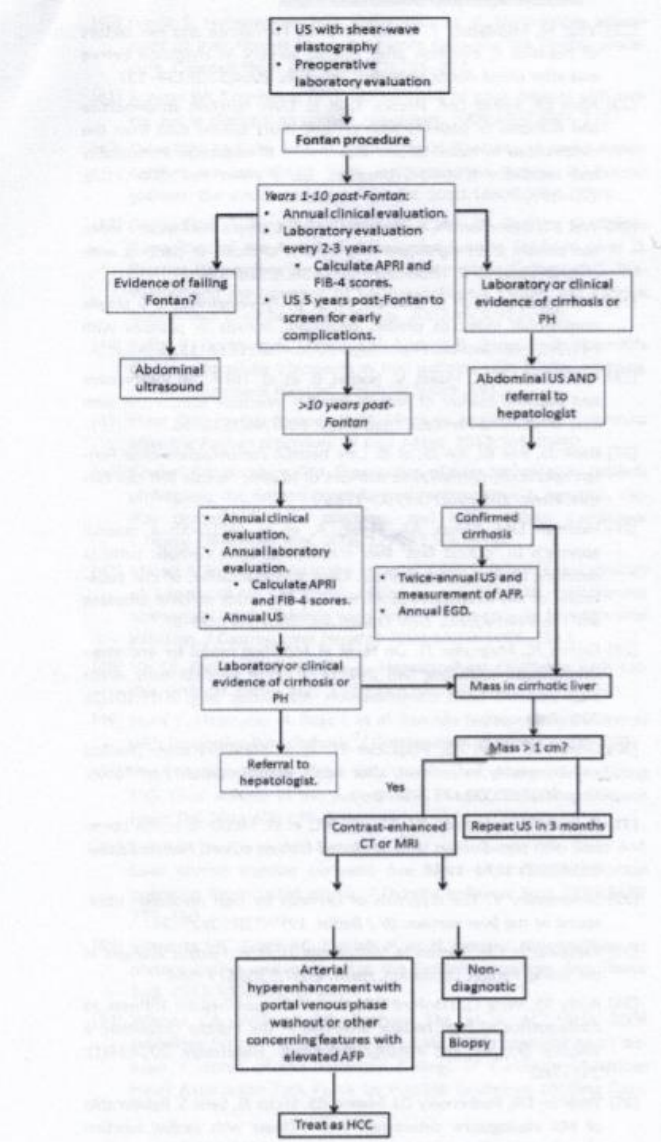


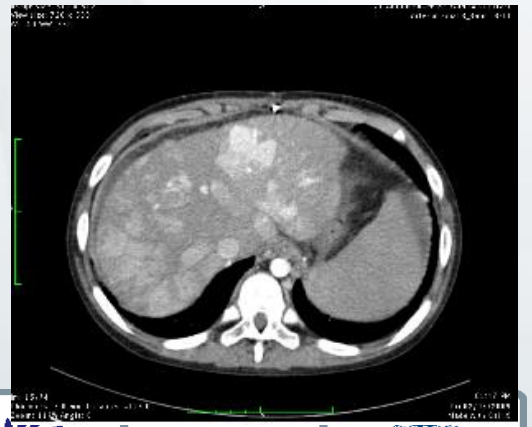
FIGURE 2 Liver surveillance before and after the Fontan procedure

- Around 1/3 of people 15 years post Fontan will have significant liver complications
- Exact timing, method and frequency of monitoring to be determined
- Will need to identify risk factors and streamline according to risk
- Consider structure vs functional uncoupling
- Combination of serum markers/ultrasound and Fibroscan for monitoring More invasive investigations eg CT, scopes if abnormalities identified

Hilscher et al Surveillance for liver complications after the Fontan procedure. Congenital Heart Disease 2017;12:124-132

Case

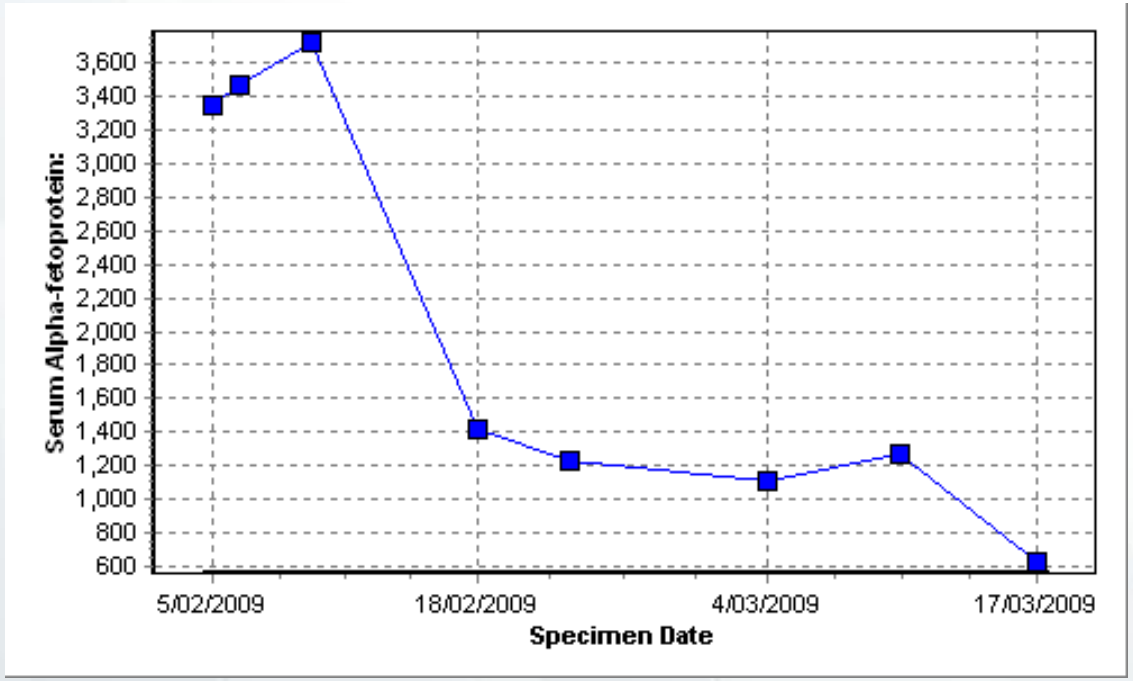
- 13 year old Fontan in China in infancy, moved to Australia at age 11.
- Presented with increasing lethargy, palpitations and SOB. ECG/ catheter: atrial flutter and a poorly functioning Fontan circulation with widely open right ventricular outflow tract (RVOT) and incompetent pulmonary valve, severe tricuspid regurgitation and PA mean pressure 11mmHg.
- underwent a tricuspid valve closure, extra cardiac Fontan and pulmonary valvuloplasty with Cox Maze procedure to treat atrial arrhythmia. A permanent pacemaker was also inserted.
- 18 months later, developed persistent RUQ pain, fever of 39°. Anicteric, hepatosplenomegaly and a large, smooth, firm mass palpable on R , splenomegaly
- Ultrasound: cirrhosis, splenomegaly, HV grossly distended.
- Triple phase CT- cirrhotic changes with several areas (especially segment 4a and 2) of intense arterial enhancement and washout consistent with HCC
- AFP 3340 ug/L [0-12].
- Extensive investigations to look for other causes of cirrhosis
- Tumour extent and extension into PV, precluded resection and transplantation



Rosenbaum J, Vrazas J, Lane GK, Hardikar W. Cardiac cirrhosis and hepatocellular carcinoma in a 13-year-old treated with doxorubicin microbead transarterial chemoembolization J Paediatr Child Health. 2012 Mar;48(3):E140-3.

The case cont..

- Rupture of tumour with haematoperitoneum
- Symptomatic +++ ascites, pain
- Used chemoembolization with doxorubicin coated beads X 2
- Good tumour lysis
- Left eye blindness (hepatic AV shunts and PS collaterals)
- Survival 6 months, good symptomatic control
- Returned to China for OLT
- Deceased within months of OLT



The End

Measuring and Monitoring for Portal hypertension

- Protein losing enteropathy - AAT clearance
- Ascites- differentiate cardiac vs liver maybe difficult (SAAG, Protein content of ascites, Serum BNP>500pg/mL(cardiac) unreliable if both and renal disease, **HVPG: normal in cardiac elevated in liver**)
- Varices- screening endoscopy in all patients with cirrhosis. Program of Banding or B blocker fro high risk varices
- Liver failure markers all confounded: Albumin (PLE, intake), INR (anticoagulants), ammonia (PS shunts)

Liver complications of long term Fontan circulation: **Hepatocellular cancer**

Presenting Stages of Hepatocellular Carcinoma

Presenting Stage	# of Patients	Outcomes	# of Patients
Single tumor < 5 cm	10	Deceased before 1 year	8
Single tumor > 5 cm	4	Alive at 1 year	14
Multiple masses	4	Alive at 5 years	13
Metastatic Disease	7	Alive at 10 years	0

Dickmeyer et al AASLD Nov 2015 presentation