PATRICK KAMATH: Good afternoon, everyone. For the new Fellows who don't know me, I'm Patrick Kamath. I'm one of the hepatologists. For the old Fellows who know me well and see me only in a white coat, this is just to show you how I do own a jacket. OK.

So I don't have much data to present. I just want to present different manifestations of the liver in heart disease. And this is more of an approach. There are not too many studies that have been done.

So when we talk with the liver and heart disease, we are talking about cardiac manifestations of liver disease. We are talking about conditions for the heart and the liver involved by the same disease. And I'll go over these two aspects briefly and spend most of my time on hepatic manifestations of cardiac disease.

So if you look at cardiac manifestations of liver disease, basically cirrhosis is a hemodynamic problem. So that when patients have advanced liver disease, they have high cardiac output and low peripheral resistance. So you'll see that in every patient.

Additionally, there are some pulmonary vascular complications that occur. There is hepatopulmonary syndrome, which is predominantly a gas exchange problem. That's not what we're going to talk about today.

The hemodynamic problem, which is from the lungs, is portopulmonary hypertension. And if long-standing, can result in right heart failure and sometimes death.

So what are the clinical correlates of portopulmonary hypertension? How common is it?

In liver transplant centers, 5% to 10% of patients have portopulmonary hypertension. And it also occurs in pediatric groups. There is no correlation with portal hemodynamics. It's not related to the amount of portal pressure. There is no correlation with the type of liver disease. In fact, you don't even need to have cirrhosis. You just need to have portal hypertension. So you can get it with portal vein thrombosis. No correlation with severity of liver disease, as assessed by the CTP or other MELD scores.

What we are now finding-- and this is a paper which Jay wrote as published in*Gastroenterology* at the end of last year. We find that there are a lot of spontaneous porto-systemic shunts in these patients. And the larger the shunt, the higher the pressure and the less the response to treatment.

For instance, you see here is one of our patients-- a large spontaneous porto-systemic shunt. Typically they tend to be splenorenal shunts. So we believe-- if pressure equals flow times resistance-- patients get pulmonary hypertension because these large shunts increase pulmonary flow and there are vasoactive substances which come from the spleen. And you know the spleen breaks down platelets. We think there are some vasoactive substances which get entered into the circulation, and they cause portopulmonary hypertension.

The proof, of course, would be if we occlude these shunts and we reverse pulmonary hypertension. And we've done that only in one patient so far.

So what is our current practice for portopulmonary hypertension? It's not generally an indication for liver transplant. There are five centers in the United States which are now doing liver transplant with portopulmonary hypertension as an indication. We are one of them. And that's largely because of Mike [INAUDIBLE], who is really the world expert in this area. But generally more centers are not doing liver transplant for this.

And when we do a liver transplant, we want low pulmonary pressures. Because once you have high pulmonary pressures, the mortality is exceedingly high. So if you do it in children and if you do it early enough, you can reverse portopulmonary hypertension. If you do it once the mean pulmonary arterial pressure is very high, then those vessels are already remodeled and you don't hold them a great deal. So this just very briefly about portopulmonary hypertension.

There are also conditions where the heart and the liver are involved by the same disease. And when we talk about that, typically it's alcohol amyloidosis and hemochromatosis. There are multiple congenital abnormalities of the liver which are associated with cardiac disease, but those are not really involved by the same disease. They are just associations.

So the practical issue is this. And this is the question we asked him. He was one of our medical students who was working with us. So he said if you have alcohol, amyloid and hemochromatosis in one organ, and you also have involvement of the other organ, how likely is it that it's related to the same condition?

And the interesting thing here is-- this is only based on biopsy-- is that specific organ involvement with one disease does not imply similar involvement of the other organ. So in about half the patients, if they had amyloidosis of the liver, the cardiac condition was related to something else, typically ischemic heart disease. And the same thing with hemochromatosis. So if you get heart and liver disease, don't straight away assume that they're related to the same condition. It may be something else.

And now for the main talk of today, which is hepatic manifestations of cardiac disease. So let's start with a case. The white liver-- Jonathan, this is a patient you used to look after. Doug McGill saw him and I saw this patient in Doug's absence. He's written many large checks to Mayo. So a 73-year-old male, myocardial infarction, ventricular tachycardia, AST and ALT elevated, alkaline phosphatase. CT Scan showed a white liver. CT of the chest showed fibrosis.

And see, white liver. No contrast here. OK. White's clean. Look at the lungs-- fibrosis in the lower part of the lung. You can see the wires here of the previous cardiac surgery.

So the question here is 73-year-old male, previous myocardial infarction, ventricular tachycardia. CT scan shows a white liver. CT chest shows fibrosis. What are the causes of a white liver in a CT scan?

Who's not eating? Monesh? White liver on a CT? Absolutely diagnostic.

And what is the most likely cause in this patient? The liver looks like it has contrast, but you have not given contrast. Anyone? Yes, I heard. What did you say?

AUDIENCE: Glycogen--

PATRICK KAMATH: Glycogen storage disease-- good, that is one possibility. When glycogen fills the liver, the liver attenuation characteristics are changed and it becomes white. Anything else? He's 73 years old, remember.

OK, so amiodarone. When a patient is on amiodarone, at the end of a year, the liver is going to be white. So don't get worried. And why is this? The normal iodine requirement for a day is 150 micrograms-- maybe up to 414 different parts of the world. Amiodarone is 37.3% weight-- by weight iodine.

And so the typical dose of amiodarone is 400, so you get 150 milligrams per day. And at the end of the year, iodine represents 1% of the weight of the liver. If the weight of the liver is 1,500 milligrams, this is 1.5 grams.

If you look at contrast like Omnipaque, it's 300 milligrams of iodine per milliliter. You are normally given 20 milliliters, so that's 600 milligrams. So the end of the liver-- end of a year when a patient is on amiodarone, you've nearly got the equivalent of three contrast studies, and that's the reason the liver becomes white.

Heavy metals also cause a white liver-- hemochromatosis, gold, Wilson's-- this is just an aside-- glycogen storage disease, Garrett told us, and thorotrast. Garrett, why don't you try the second-- hemochromatosis-- liver is white. What about the spleen?

AUDIENCE: [INAUDIBLE]

PATRICK KAMATH: The spleen is not white. OK? So hemochromatosis, the liver is black. Is there any type of hemochromatosis where both the spleen and the liver will be white?

AUDIENCE: [INAUDIBLE]

Very good-- ferroportin. Why is that?

AUDIENCE: [INAUDIBLE]

PATRICK KAMATH: So typically in hemochromatosis the extra iron is in the hepatocytes. In ferroportin, it is in reticular endothelial system, and that's why both the liver and the spleen get white.

OK. So white liver, patient with heart disease-- not likely to be hemochromatosis. Think of amiodarone.

So when we look at liver dysfunction and cardiac disease, we're dealing with drugs. We are dealing with viral hepatitis, transfusion-related iron overload. And viral hepatitis and transfusion-related iron overload occur in about 10% of patients.

Our major talk is going to be on congestion, ischemic hepatitis, and congenital heart disease. But just a little data on viral hepatitis.

So these are data from the CDC. They've looked at patients who have had congenital heart disease. And these are blood samples that have been stored. If you had surgery before 1992, approximately 10% had HCV antibody positive, 4% had RNA positive. And according to them-- there are 192 patients studied-- only 1 had an elevation in the AST and ALT.

We have seen much more severe problems related to hepatitis C than this. But in general, any patient you are going to see for whatever reason who has had cardiac surgery before 1992, you must do an HCV on these patients.

Now the main problems that the liver encounters in cardiac disease is either congestion or ischemia. And if there's one slide you need to remember today, it is this slide. Because this is the basis for why the liver gets hurt in cardiac disease.

The liver is highly metabolic. It is the most active organ in the body. And it requires 25% of the cardiac output. The hepatic artery provides 30% of the hepatic blood flow with about 60% of oxygen to the hepatocytes. The hepatic artery also provides 100% of oxygen to the bile ducts.

The portal vein, on the other hand, supplies 70% of hepatic blood flow, but about 40% to 60% of oxygen to the hepatocytes. So both the hepatic artery and the portal vein are supplying oxygen to the liver.

When you have right-sided cardiac failure, there is very little portal blood flow. So in right-sided cardiac failure, you're already dealing with a slightly hypoxic situation. And the hepatocyte which is normally so highly metabolic, is vulnerable to hypoxic injury because of its high metabolic rate. So anything that you do to impair blood flow to the liver has its consequences.

And so what are the consequences? You can have two patterns-- one is congestion and one is ischemic. So the clinical presentations of congestion would be either acute or chronic. And the same thing with ischemia-- it could be either acute or chronic. Unfortunately in many patients, you may have an overlap of acute and chronic of both ischemic and congestion patterns.

OK. So acute hepatic congestion-- when do you get it? Acute tricuspid regurgitation-- anyone? What's the most common cause of a acute tricuspid regurgitation in adults?

AUDIENCE: It's infected--

PATRICK KAMATH: Good. Due to what?

AUDIENCE: IV drug use.

PATRICK KAMATH: IV drug use-- very good-- In fact, acute endocarditis. So right ventricular infarction, right atrial thrombus-- so the clinical picture is of an acute Budd Chiari syndrome. That is, they have discomfort in the right upper quadrant, the liver gets big, and they have ascites.

So when I see patients with suspected Budd Chiari or cardiac disease, my physical exam-- the size of the liver doesn't help me. But I press over the liver. If this is going up, then we know that the hepatic veins are open. So typically the hepatojugular reflux is present and it's a pulsatile liver. And when it's acute, the bilirubin elevation is higher than in chronic. And the AST and ALT are usually five to eight times the upper limit of normal.

Your differential diagnosis is easy. Imaging will help you. Budd Chiari, the veins are occluded. In cardiac failure, the hepatic veins are dilated-- so typically large veins. And both of them will give you this mottled appearance of the liver, which is a perfusion defect. Additionally, in cardiac failure you have bilateral pleural effusions.

Anyone, diagnosis here? Let's go to the back. Craig, what's your diagnosis here? What is the cause of this acute cardiac failure? What is this here?

CRAIG: [INAUDIBLE]

PATRICK KAMATH: No, that is the outside. This is within the-- anyone? It's a large something in the lumen of the atrium.

AUDIENCE: [INAUDIBLE]

PATRICK KAMATH: Good, Amindra. It's a right atrial myxoma causing acute right-sided failure. OK?

So is that clear about acute congestion? Chronic is really not that much different.

OK who's going to take this one? Benny?

A 58-year-old male came to us from a cardiologist of a major university hospital for evaluation of ascites. No risk factors for liver disease or malignancy. They have done echocardiography twice on the outside. It was reported normal. We found ascites, nothing for liver disease. Labs were normal-- albumin was 3.9 and ascitic fluid was 1.5. So a large-- high gradient. Cells were 150. What do you want to do? They say no cardiac disease? You look, and you don't think it's liver disease.

BENNY: So you have [INAUDIBLE] of ascites. I would still suspect a heart attack.

PATRICK KAMATH: OK. So what do you do?

BENNY: I go examine him.

PATRICK KAMATH: What's that?

BENNY: Examine him.

PATRICK KAMATH: Examine him.

BENNY: [INAUDIBLE].

PATRICK KAMATH: Yeah, we were convinced. But the cardiologist on the outside was not. So we have to do something else. So we cannot pull rank on a cardiologist.

BENNY: [INAUDIBLE]

PATRICK KAMATH: So I'm a great believer in measuring pressures. So we measured pressures-- just minimal portal hypertension, but really high right-sided pressures. The biopsies confirmed that. The CT of the chest, which is a very good test for constrictive pericarditis, and he went home and had a pericardiectomy.

So when patients come with ascites, you're not sure whether this is liver disease or cardiac disease. I like to use hepatic wind pressure gradient. And I know Ritchie and I have talked about this really being very useful to us clinically-- not so much in measuring pressures as a response to beta blockers.

So the hepatic vein pressure gradient measures sinusoidal pressure, but it's very useful in determining causes of ascites if you have cardiac failure, no portal hypertension, and elevated free pressure. So if you've got a ascites, HVPG is normal, you say OK, this is likely cardiac disease.

But if you've also got elevation in the HVPG and the free pressure, then you said this is really longstanding cardiac disease. Not only do you have cardiac failure, but now you also have cardiac cirrhosis.

And the advantage of this procedure is it may be combined with liver biopsy. And so I know both Ritchie and I have a low threshold for measurement of this and liver biopsy when we have undiagnosed ascites.

So chronic hepatic congestion-- like acute, just a little longer. The liver labs change a bit, and the liver labs are important here. Hepatomegaly continues to be pulsatile. It tends to be an indirect hyperbilirubinemia. This is the interesting part, or really interesting to me. It's indirect in about 70% of patients. And I'll tell you why I think this might be the case.

It proved to be related to decreased uptake, maybe some hemolysis. But even in the absence of hemolysis, you'll see this indirect bilirubin. It tends to correlate with prognosis. And the higher your right-sided pressures, the higher the bilirubin. You get AST and ALT elevation in about 1/3 of patients, typically about three to five times. Remember, the acute congestion-- it tends to be higher. You get a decrease in the albumin. And if you look at a single test in these patients, it's the prothrombin time which tends to be prolonged.

Everything else seems OK, and the prothrombin time seems to be prolonged, which makes me think that the liver is sick. The AST and the ALT are not picking that up. And a test like uptake of bilirubin is impaired. And synthesis of that cell is impaired. And that's why the prothrombin time tends to be prolonged.

So that-- if you're looking for liver dysfunction, it's not just the AST and ALT that are going to help you.

So we deal with acute congestion, chronic congestion. Now the question is acute ischemia and chronic ischemia.

So who should I get next? Art--

49-year-old ambulant patient with a one-day history of right upper quadrant pain. Comes with AST 850, ALT 920. Two days later, AST and ALT are close to normal. Your diagnosis?

ART: [INAUDIBLE]

PATRICK KAMATH: You go for?

ART: A, ischemic hepatitis.

PATRICK KAMATH: Do you want to go for B?

ART: Yes. [INAUDIBLE]

PATRICK KAMATH: OK. So we are just going over acute rises in AST and ALT. So in acute ischemic hepatitis, don't think of this condition if they don't have right-sided failure. 90+% have right-sided failure, because then there is no portal blood flow. So 50% of the oxygen is shut off. So you're living on hepatic artery flow. Then something happens which decreases cardiac output. So that's hypertension for whatever reason, or an arrhythmia, and zone 3 gets infarcted.

So the typical enzyme pattern is it goes up into the thousands. In seven to 10 days, it comes back into the 200 to 300 range. So it's got to be a sick patient who gets this. The ambulatory patients are not likely to get ischemic hepatitis.

And the treatment is of the underlying cardiac disease. And some of them can actually get fulminant liver failure.

So there are criteria for ischemic hepatitis. And these criteria are reversible elevation of the AST and ALT. You exclude other causes, appropriate clinical setting, and the AST and the ALT are very high.

So my next question is-- maybe Ashmani, -- AST/ALT 10,000. What's your differential diagnosis. It's very small.

AUDIENCE: Ischemia--

PATRICK KAMATH: Ischemia, 1.

AUDIENCE: Acetaminophen.

PATRICK KAMATH: Acetaminophen, 2. Very good--

AUDIENCE: [INAUDIBLE]

PATRICK KAMATH: --which one?

AUDIENCE: [INAUDIBLE]

PATRICK KAMATH: 10,000--

AUDIENCE: [INAUDIBLE]

PATRICK KAMATH: Each is 3. So bilirubin not elevated, and that's elevated. Number 4-- there are only 4 conditions.

AUDIENCE: [INAUDIBLE] stone.

PATRICK KAMATH: Stone is not 10,000 range. Number 4-- Nathalia, you and I saw this patient.

AUDIENCE: [INAUDIBLE]

PATRICK KAMATH: That's the ferritin is very high. Patient seen in neurology. Anyone?

It's from muscle. So status epilepticus-- so muscle injury-- so when neurology calls you, and AST and ALT is high, tell them it's not a liver problem. It's released from muscle. OK. So your differential diagnosis of an AST and ALT greater than 10,000 is very small.

The term ischemic hepatitis is still kept, even though they don't have much inflammation. It's not much of a hepatitis, but we use that term ischemic hepatitis or hypoxic hepatitis. The term "shock" liver is preferably not used because only about half of them have a shock. So don't use the term "shock." Use ischemic hepatitis.

Why hypoxic hepatitis? Because when patients have really bad sleep apnea, they can get exactly the same clinical picture. But you make the diagnosis only if there's right-sided cardiac failure.

Additional clues in these patients is you check the LDH. So the ALT:LDH ratio, because the hypertension-- muscle is damaged. The heart is also damaged. This is not fractionated LDH. LDH 5 is liver. LDH 1 is heart. So if you measure total LDH, if the ratio is less than 1.5-- meaning the LDH is elevated more than this-- it's more like hepatic ischemia. Whereas viral hepatitis, ALT is much higher than the LDH.

But following the acute phase, you get the cholestatic pattern and this reflects the chronic ischemia. And they can have prolonged cholestasis, again, because of a low cardiac output. There's not much you can do from our side. Chronic hepatic ischemia-- low cardiac output. They have about 15% to 20% typically. And the bilirubin sometimes is really very high. And remember we said hepatic artery flow is to the bile duct? So you see alkaline phosphatase changes. And that's the reason for the cholestasis.

But this is-- this condition I find always difficult to convince the cardiologist of. They know about congestion and the liver. You tell them it's low output. They say no, the liver is bad. And you say no, the liver is OK. The heart is bad. This is difficult to convince them that low output is the reason for such high bilirubin elevations.

I think we've got five patients-- Peter Brady in cardiology looked at this-- we've got five patients with aortic stenosis, with high bilirubin, four [INAUDIBLE] valvuloplasty-- we had decreased. OK, I think this is correct.

The other time the cardiologist is going to call you is because after cardiac surgery they tend to have problems. So you can have acute ischemic hepatitis picture. You can have just hyperbilirubinemia because of cholestasis. Low output-- they tend to be on TPN that, again, causes elevation of the bilirubin. And they may be septic.

The AST and ALT elevations following surgery are variable. And this may be related to the anesthesia too. They get ascites due to fluid overload. Then if they've got ascites and they've been in hospital for three to four weeks in the unit, everyone is focusing on the liver. Remember that this is the time they start getting constrictive pericarditis following surgery. And there's been one patient in whom we've diagnosed constrictive pericarditis.

If you have a CAT scan and you want to know constrictive pericarditis, Jerry Breen is the radiologist to call. He's the expert. He's got the world's largest series of constrictive pericarditis diagnosed at ERCP. So in ERCP pictures, he has diagnosed two constrictive pericarditis.

Now here is what we're continuing to see. And whoever is on the consult service knows about this. So LVADs associated with cholestasis. So these are the left ventricle assist device. They go in for surgery. Low cardiac output-- the device is put in, cardiac output increases, and then the liver goes bad. And the best indicator for 90-day and 1-year mortality-- one of our cardiology fellows has looked at this-- is hyperbilirubinemia.

So they are dying because something happens in the liver, and I'm not quite sure why. I'm not sure whether it's a reperfusion-type injury or whether it's just low cardiac output not recovering. But you are going to see these problems. I'm not quite sure what we do about these patients.

The second part of the talk was supposed to be given by Sumeet. But since he cannot come here today, we'll talk about congenital heart disease in the liver. And for those who are finishing your fellowship now, this is going to be a huge problem for you. And I'll tell you why in a bit.

So here's a patient who is actually getting a chemoembolization today, a 31-year-old female with complex congenital heart disease. We'll talk about the Fontan in more detail. And she was doing fine. Last year she started getting recurrent deep vein thrombosis.

And then as part of imaging, she was found to have liver masses. Alpha-fetoprotein is 893. CAT scan-- I don't see it well from here, but that was supposed to be-- I don't see it well from here. That is supposed to be a hyper enhancing mass. That is the washout. This is the mass on angiography. And that is a hepatocellular carcinoma. She also has multiple other vascular lesions, which makes the diagnosis of hepatocellular carcinoma in these patients very difficult.

So when we talk about congenital heart disease in the liver, we'll talk about the Fontan procedure because this is the one associated with the biggest liver problems. We'll talk about why you'll get this and how they present. And we'll close by how you approach hepatic disease in patients with cardiac disease, but specifically with congenital heart disease. And also about how we plan surgery in these patients.

Right now-- when I was in medical school, with complex congenital heart disease we used to say that these are patients in whom survival into adulthood is unlikely. Currently if you get complex congenital heart disease, you tell the parent that they've got an 85% chance that they're going to survive into adulthood. So cardiac surgery has become so good. The problem is with all the procedures that are done, the liver tends to bear the brunt of all of those problems.

And so right now it is estimated that there are about 1.3 million patients with congenital heart disease. About 1 in 150 adults in the US has some form of complex congenital heart disease. And Carole once led the committee which looked into this. So it is a problem, and it's going to increase.

So the Fontan procedure-- he's a French surgeon from Bordeaux. This is carried out-- don't worry about the details. Think of a condition where blood is not going to the lungs. So venous blood should go into the pulmonary arteries into the pulmonary circulation. So if you have pulmonary atresia, if you have a hyperplastic right ventricle, if you have tricuspid atresia, then blood is not going into the lungs. So these patients get cyanosed, and they have to have a small shunt somewhere.

So the Fontan procedure is a way of getting blood to the pulmonary artery-- either from the atrium directly, or from the superior vena cava, or from the inferior vena cava. So you're completely bypassing the right ventricle. So that's the Fontan procedure.

So here is the Fontan procedure. The original Fontan is where you take the right atrium and anastamose it to the pulmonary artery, and you separate out the pulmonary artery here from its root. This was a good procedure, first described 1971. The problem is this atrium gets thrombosed, and then you tend to have a problem.

So this was modified by Fontan. He did this procedure. So you connect the superior vena cava to the pulmonary artery. So the venous blood from the upper part of the body is now going to the pulmonary artery for oxygenation. Why do you do it in two phases? Because all of a sudden if you get the left ventricle-- remember, the right ventricle is not working-- you're getting double the circulation. So it's done step-wise.

So the first is called a Glenn procedure, where you connect the superior vena cava to the pulmonary artery. The second part is called the completion Fontan, where you connect the inferior vena cava to the pulmonary artery and the superior vena cava. So this way, all your systemic circulation is now bypassing the right ventricle and going to the pulmonary artery. You can have this with a conduit. You can roll up the atrium and do that-- that's intracardiac. Or you can do it as a graft, a conduit, which is extracardiac.

But see what happens here. That's the pulmonary artery. We have the liver here. So the liver is very soon going to see pulmonary artery pressures which are very high. So there's the pulmonary artery. Now when you have right-sided failure secondary to tricuspid regurgitation, there is pulsatile flow. So in systole there is tricuspid regurgitation, so the liver bears the brunt of systolic flow. But in diastolic flow-- during diastole, no pressure on the liver. So there is a little time to recover.

But the problem with the Fontan is it is nonpulsatile flow. So 24 hours a day the liver is going to see high right-sided pressures. So if you have dysfunction of this shunt, then you have liver disease. And that is why liver disease is so common following a Fontan procedure.

So what are the consequences? Here is the pulmonary artery connected to the superior vena cava and inferior vena cava, so you're going to get venous hypertension. If the shunt doesn't work, if it tends to get narrowed, or if you develop hypertension, even more pressure on the liver. So Fontan stenosis tends to be a problem.

The second is-- so remember we said two principles-- low flow or congestion. So here is the congestion part of it. Second, with time you tend to get reduced cardiac output. Remember these patients are working with a single ventricle because the right ventricle is gone.

So this right ventricle at one time is seeing both pulmonary venous flow and pulmonary arterial flow. So its work has doubled. And it's really not used to being a systemic ventricle, so that with time this ventricle starts failing. If this fails, you get pulmonary hypertension, worsening of liver flow.

So with the time, there's a problem. Remember, duration, post Fontan, determines how bad the liver disease is.

What else happens? They are on multiple drugs. I told you-- showed you amiodarone. 50% of them have arrhythmias and tend to be on pacemakers or defibrillators. They get viral hepatitis because they have had surgeries in the '70s. Iron overload, fat-- we tend to see drug and alcohol problems in these kids. You have to deal with these kids, because throughout their life they've had a problem. Their mothers are very protective. You get a lot of behavioral problems in these kids.

So in addition to all that, they have got alcoholism and drugs, which further contribute to this. I'm not saying that happens to all, but you do see it in that group of patients.

So the end result of this high pressure is a liver which looks like this. So there are two patterns post Fontan. There is a reticular pattern which is diffuse. And many believe this is a predictor of who will develop cirrhosis. And you have a zonal pattern where only portions are under-perfused. And it is believed that they don't develop cirrhosis. We don't have a serial follow-up of our patients, so we don't know.

But they get hypervascular nodules. And we'll talk about that in a bit. And of course they get cirrhosis and variceal bleeding. And previously people would say cardiac cirrhosis does not develop portal hypertension-- not true. If they develop portal hypertension, they don't get variceal bleeding-- not true. They bleed. They don't develop hepatocellular carcinoma-- not true. They do get that, and it's a big problem too.

So the duration matters. The longer post Fontan, the higher the risk of liver disease. So if you're right-sided pressures are high, more likely to get liver disease. If you're Fontan is failing, more likely to get liver disease. So that will help us determine whom we need to follow more closely.

So the 12-year follow-up here-- about 1/3 of them have liver problems. Remember I said the INR tends to be prolonged in liver disease disproportionate to other problems. So they-- about 60% of them have a coagulopathy. Remember about 1/4 will have developed cirrhosis by 12 years. And if you assume that 1 in 50 adults ultimately is going to have complex congenital heart disease, this is going to be a significant cause of cirrhosis in the future. And we also see liver masses in these patients.

So how do we manage these patients? Very difficult-- TIPs-- so they have variceal bleeding. You cannot do TIPs because right-sided pressures are high. You will kill them with the TIPs. So no TIPs in these patients.

I didn't go into it. But because of the hemolysis they tend to get stones. If you see a patient with a Fontan has gallstones, please tell the surgeon no laparoscopic procedures. Because venous return in these patients is completely passive. And you increase intra-abdominal pressure. Half the venous circulation is gone. It doesn't teach the heart. They get profoundly hypoxic during surgery. So they must have only open procedures and not laparoscopic procedures.

That are difficulties in establishing cardiac cirrhosis because we see this abnormal vascular pattern. Gastric varices treatment-- again a problem. No glue-- they tend to having intracardiac shunts. So you'll have problems. So if they bleed from gastric varices, difficult to treat these patients. We've lost a patient with gastric varices who has had glue.

Screening for hepatocellular carcinoma-- we'll come into a little more detail. And transplantation-- so there are a lot of management issues in these patients. Not quite sure when to screen, or who to screen, or how to screen. And the problem is because this is what the liver looks like.

So these are the typical Fontan livers. You have absolutely no idea which is a mass and which is not. These are the perfusions. This was a hepatocellular carcinoma in this patient. It's very difficult. So you can keep biopsying them, and you will miss the lesions. So we have tended to use an alpha- fetoprotein to help us make the diagnosis. So all seven patients who have had HCC have had an elevation in alpha-fetoprotein, which means we're probably missing a few hepatocellular carcinomas.

Why is it so difficult? The livers typically tend to be nodular, and you get hypervascular nodules that are not HCC. And what are those? They tend to be typically focal nodular hyperplasia-- those areas where you get more blood flow in one area than in the other area.

Some believe that because you've got cardiac failure, the typical arterial inflow portal washout may not occur. I'm not quite sure about that. But some people believe that.

If you have a nodule, typically we would say, let's go to an MRI. But you cannot use an MRI in about half of these patients because they've got pacemakers or defibrillators. If they've got a mass, and you think it's hepatocelluar carcinoma, you cannot offer them radiofrequency ablation-- again, because of pacemakers or defibrillators. So we have got one patient who will get a microwave, and that might be the better treatment in these patients.

What about non-liver transplant surgery? Like I said, we will avoid laparoscopic procedures in those patients. Not quite sure how best to deal with them. Remember, I said INR tends to be high in these patients. So INR and albumin do not correlate well. And while we use the MELD score, CTP and ASA class, age as predictors of outcome, none of these patients whom we studied or modeled had congenital heart disease. So I'm not quite sure what's the best way to approach surgery in these patients.

So the two questions are what about liver transplant and what about heart transplant? If you look at heart transplant in congenital heart disease, they've got associated liver disease. And I'll show you why the survival in them is not as good, because I think many times the liver disease is not diagnosed.

Cardiac surgeons don't like to do a transplant because they have got multiple sternotomies. Remember when I showed you the Fontan, I said there are different steps. You so the Glenn procedure first. Then you do the IVC. So the average number of surgical procedures that a patient with a Fontan who comes to transplant has is 3.7. So they've had multiple sternotomies, which makes it difficult for the cardiac surgeon.

Their vascular connections are all complicated. They are all changed around. Those who are coming to transplant may have hepatitis B or C. And because they've had multiple transfusions, they tend to have these PRA positive. Anyone know what a PRA is? Yan?

So these are called Panel Reactive Antibodies. So the kidney transplant and heart transplant people use this. It just tells you what percentage of the population you have developed antibodies against.

So generally, if you've developed more than 50% antibodies, it means that you-- only half the organs available you're likely to get. So the patient I'm talking to you about has got a 90% PRA positive. So it will be extremely difficult to get a heart for her. If you put in the liver beforehand, there is an advantage. But we won't get into those details.

So they're difficult to transplant. Because of the multiple transfusions, it means they've already developed these anti-human antibodies. So it's difficult to find a good organ for them.

So the isolated cardiac transplant post Fontan-- if we see the outcomes in these patients-- we should have another curve in there-- it's about 12% to 15% lower than for other indications. And when Sumeet and I were looking at this, we thought really, I think they were missing cardiac cirrhosis in these patients. We have missed it here too.

So I think the reason they do a little worse is because we have not picked up the liver disease. The complications here-- the sepsis, the multiple organ failure-- are typically what we see in cirrhotic patients who have undergone surgery.

So what is your take-home message? If you see a patient with cardiac disease and abnormal biochemistry, and ascites, what would you do? And if you're planning surgery, what are you going to do?

So abnormal liver biochemistry-- simple enough. We always look at symptoms. We try and see if there's evidence of cirrhosis. We see if there's evidence of portal hypertension. We do labs, try and get the pattern. See is this ischemia, which is low output-- or venous congestion, which is high right-sided pressure?

Occasionally, I told you, you can get stones in these patients. Once we know the pattern of injury, then we try and find out the etiology. We find out whether it's primary cardiac, which is related to failure or ischemia. Or we find out whether it's secondary to treatment.

So typically congenital heart disease, the liver problems are secondary to the surgery. Or it may be related to the blood or the drugs, or it's related to clotting problem. And don't forget that these patients can have primary liver disease. And that might be, again, related to viruses.

What about ascites? Again, is this cardiac or is this liver? That's our first question. So we'll do a serum ascitic fluid albumin gradient. If it's pointing more towards cirrhosis, remember we talked about pressures. Look for viral hepatitis, drug, iron overload, other diseases. There are other problems which contribute to the ascites in these patients. And I have really not gone into that.

So if you think the cardiac problem is the only problem that we deal with in congenital heart-- no, they have a protein losing enteropathy. Again related to high pressures-- the lymphatic pressures are very high. They have a protein losing enteropathy. And this is the treatment that I do not understand. Currently they are all treated by cardiologists because most gastroenterologists don't see these patients. The treatment of choice for protein losing enteropathy following Fontan or patients with Epstein is infliximab. I have no idea how that works. But they are using infliximab. They think that's better.

Ed, what do you think?

ED: I don't understand the mechanism involved.

PATRICK KAMATH: But they say the best results they have got is with infliximab. So again I-- they tried octreotide before, which seemed to help a little. But now it's fashionable to use infliximab in this first. I don't quite understand why.

But anyway, so they tend to have other problems. They can have malignancy too. But if you are thinking of primary cardiac dysfunction, again, if it's surgery related, we want the cardiologist to look back. If the conduit, which is a Fontan, is stenosed, this is probably the easiest to deal with because you can just stretch it out or put a stent in there. And don't forget constrictive pericarditis. Always consider constrict pericarditis as a cause of ascites in these patients.

If these patients with congenital heart disease and cirrhosis require surgery, what is our proposed approach? We don't have data to support that this approach is the best. But this is how we are dealing with this. If they have got child A cirrhosis, low MELD score, we say don't worry about the liver, go ahead with your cardiac surgery.

The score is between 12 and 18, we think they should be evaluated for liver transplant. You can proceed with cardiac surgery, and liver transplant if failure occurs after cardiac surgery. Again they are proposed. We have not validated this.

And I think if you have an HCC, or if your child C cirrhosis MELD grade is greater than 18, I think these patients require a combined heart and liver transplant.

I just want to acknowledge a few people. Sumeet and his wife Nina have been working on this. Carole Warnes and Sabrina from cardiology have been helping us out, because they sent us the patients. Deb Freese knows a lot about the pediatric aspects of these patients. So she's been helping us. Our liver transplant team, who are very enthusiastic about doing liver transplants and combined heart and liver transplants in these patients. Our cardiac surgeons are very unenthusiastic about doing heart transplants in these patients. And Phil Young and Jeff Fidler, the radiologists, are trying to figure out simple ways to figure out which of these nodules is a hepatocellular carcinoma and which is not.

OK, questions?

[CLAPPING]

Michael?

MICHAEL: If you can go back a couple slides to the algorithm-- back--

PATRICK KAMATH: This one?

MICHAEL: One more. So this is very logical if it makes sense, and the appropriate, you know, columns are available. But if the patient with congenital heart disease with ascites also had signs of heart failure, what is the likelihood that there is a primary liver problem? I'm thinking--

PATRICK KAMATH: Very small.

MICHAEL: Right.

PATRICK KAMATH: Except if they have had hepatitis C.

MICHAEL: Right. So can speak for that rather easily. So the algorithm actually becomes relatively less complicated if the patient has established heart failure. Would you think that that's correct?

PATRICK KAMATH: In fact, if we-- you know, this is the approach, but if we look at the patients we have seen, I would say 90+% are here, the vast majority.

MICHAEL: So well, it seems to state, you know, if it smells like heart failure, if it looks like heart failure, and you can actually see the JVP, think about the heart before the liver. That may be sacrilegious in this meeting.

PATRICK KAMATH: No, it's not. But the reason why we have this is you have to look at it from the people who refer these patients. So they typically come from cardiac surgery who do not believe that the surgery is not going right. So it's always to look for a little problem. The number of biopsies, the pressure studies we have to do, is higher than we would require.

So this is a-- so if a patient has to have a cardiac transplant and has ascites, we say it's liver disease. They say no, we won't transplant the heart unless we are convinced on biopsy that it's not the liver.

So the algorithms are for a cardiology audience. And it's-- so it's very interesting how we deal with cardiologists. So we have a liver transplant and there's bad coronary artery disease, they'd say no problem, go ahead with the liver transplant. The heart can take it. But if they require a heart transplant, and the AST is 45, they say no heart transplant because the liver is not good.

You know, so these algorithms are really related to them, not for us. For us, you're absolutely right. Most of them will be related to cardiac disease.

Joanna?

JOANNA: [INAUDIBLE]

PATRICK KAMATH: In France they have a rule that the person who did that congenital heart surgery cannot be the heart transplant surgeon. Because if you are the same person, you're never willing to say look, my surgery was really not good enough, and I need to fix the heart. That's not in the US. In the US, we are the same group. So it's a little more difficult to say that the heart needs to be fixed.

Jay?

JAY: [INAUDIBLE] thinking about. Now that we have some knowledge [INAUDIBLE] I don't know if that includes what happened. If the patient is developing progressive liver disease and not waiting until there is cirrhosis to identify [INAUDIBLE], can there, maybe, be an opportunity then to say should you think about cardiac transplant before you go in for your second or third sternotomy. Have you guys thought about this?

I mean, I know there's even less data on this. But I'm curious to know if you brought that up with the cardiologists [INAUDIBLE] Because I think it's key, right? If you just keep cutting people open when you keep saying oh, they're developing progressive liver disease, you're never going to sort of solve this problem by fixing the heart and not the liver.

PATRICK KAMATH: So the question is, should you do heart transplant earlier? And that's because each surgery makes the heart transplant more difficult, more transfusions, more antibodies. I think that's right. But again, it's the same group who are doing the cardiac surgery and the cardiac transplant. So typically they say we can't fix it. But if you look carefully, the pressure changes are really very small.

The larger question is can you diagnose liver disease early in these patients? So what we've worked out at least is this. So that 10 years post Fontan, if everything is fine, they start getting screened. So we'll see them, and we'll get an ultrasound at least on them. If your Fontan is doing badly, then it's five years that we can screen.

So the radiologists are trying to work out an MRI, which typically they do a heart MRI in these patients. But they use gadolinium. If we want FNH, we need to Eovist, so there's a problem with that. They're trying to work out a single scan which will help get that done.

Jonathan?

JONATHAN: [INAUDIBLE]

PATRICK KAMATH: This is a good question. So Jonathan's question is how frequently do we see them a year?

In 2010, I would have said Fontan would have hepatocelluar carcinoma only if they had hepatitis C, which is what I had seen. Last year-- so in 13 months I have seen 6 hepatocelluar carcinomas related to Fontan. So Carole Warnes is sort of an international expert on this. So we have 800 Fontans on follow-up here. There are 4,000 within the United States. So we see about 1 in 5 of the Fontans in our cardiology area in here.

The surgery was started in 1971. That was when the first-- but got popular in the United States in 1980. So the patients are now 20 to 30 years old. And I think this is when we're going to start seeing the cirrhosis. So we're going to-- just going to see more of them.

I see a lot of them just because of the referral practice. But anyone who has done the hospital HP consult, I think every time you go there's at least one of these patients on the cardiology service. So there are a lot of them. There's enough that cardiologists are thinking of a combined clinic. So--

JONATHAN: Yeah.

PATRICK KAMATH: Thank you.

[CLAPPING]