Doppler ultrasound and other imaging modalities before and after liver transplantation. When life depends on the liver
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Summary and Conclusions

SUMMARY

In liver transplant candidates it is essential to determine the patency and size of the extrahepatic portal vein, to search for pathology or an anomaly of the inferior vena cava (IVC) and to obtain information about the anatomy of the hepatic artery. A narrow or thrombosed portal vein and an absent or anomalous IVC may preclude orthotopic liver transplantation (OLT) or may require a modification of the standard surgical procedure; a vascular anomaly of the hepatic artery may influence the surgeon's approach during graft rearteriization. Postoperatively, serious medical and surgical complications can threaten both graft and patient survival. The major causes of hepatic graft dysfunction and failure are vascular thrombosis or stenosis, biliary complications, rejection and localized or systemic infection. It is of particular importance to differentiate clinically between rejection and biliary or vascular complications.

This thesis discusses the role of imaging modalities in the preoperative assessment of liver transplant candidates and in the evaluation of potential complications after orthotopic liver transplantation (OLT). Particular attention has been paid to the diagnostic possibilities of Doppler ultrasound.

Chapter 1 begins with the introduction.

Selective angiography involves increased risk for children and may cause vascular complications. In Chapter 2 we determined whether selective angiography is still necessary for viewing the portal vein and hepatic artery in children with end-stage disease.

Doppler ultrasound, abdominal aortography and selective angiography were performed and interpreted independently in 62 children (median age = 1 year 3 months) with end-stage liver disease, who were candidates for OLT.

Selective angiography agreed with the Doppler ultrasound findings of patency, flow direction and diameter of the extrahepatic portal vein in 84 %, 73 %, and 79 % of the children, respectively.

Important additional information was obtained from selective angiography in only five out of the 62 children (8 %). Selective angiography showed an anomaly of the hepatic artery in 21 out of the 62 children (33 %). In 18 of these 21 children (85 %), an anomaly of the hepatic artery was already visible on the abdominal aortogram.

Therefore, selective angiography did not play any significant role in the detection of an anomaly of the hepatic artery. It should only be done if the Doppler ultrasound findings of the portal vein are inconclusive or if abdominal aortography cannot provide reliable information about the hepatic artery. For the evaluation of the portal vein and hepatic artery, we recommend Doppler ultrasound and abdominal aortography, a less invasive angiographic procedure.
A survey of the blood flow in the inferior vena cava (IVC) should also be made routinely with Doppler ultrasound before OLT.

In Chapter 3 we determined the accuracy of Doppler ultrasound in the assessment of pathology or an anomaly of the IVC. Doppler ultrasound was performed in 60 pediatric liver transplant candidates. The findings were retrospectively correlated with the results of cavography (n = 9) or the peroperative findings during OLT (n = 51).

In 56 out of the 60 children (93 %), Doppler ultrasound correlated well with cavography or the peroperative findings, but there were three false-positives and one false-negative (sensitivity 80 %, specificity 95 %, positive predictive value 57 %, negative predictive value 98 %). Accuracy can be improved significantly if both the retrohepatic segment and the suprahepatic segment of the IVC, including the junction with the right atrium, can be visualized.

Doppler ultrasound is the method of choice, but cavography is necessary if the upper part of the IVC cannot be well-demonstrated.

Since the first orthotopic liver transplant at the University Hospital Groningen in 1979, patients have been undergoing routine angiography according to our post-transplantation protocol. In Chapter 4 we reviewed and described the angiographic findings in these patients at discharge 2 months after OLT and at follow-up 1 year later. In addition, we determined whether any significant changes occurred at the anastomotic site of the hepatic artery and portal vein.

Routine angiography 2 months postoperatively and at 1 year follow-up demonstrated a normal anastomosis or low-grade stenosis in 82 % and 84 % of the patients (hepatic artery), and in 88 % and 84 % (portal vein), respectively. High-grade stenosis occurred in 9 % and 5 % of the patients (hepatic artery), and in 3 % and 5 % (portal vein), respectively. Hepatic artery thrombosis (HAT) and portal vein thrombosis were observed in 2 and 7 patients and in 1 and 3 patients, respectively.

In the vast majority of patients (76 %) the anastomotic site of the hepatic artery did not change significantly. In 8 patients a normal anastomosis, or low or medium-grade stenosis developed into high-grade stenosis or thrombosis. Conversely, in 9 patients medium or high-grade stenosis developed into a normal anastomosis or low-grade stenosis. In all 8 patients who initially demonstrated high-grade stenosis, the hepatic artery proved to be patent at 1 year follow-up.

In almost all patients (98 %) the anastomotic site of the portal vein did not change significantly. In one patient, who initially demonstrated a normal anastomosis, thrombosis was found at 1 year follow-up.

In most patients, routine angiography 2 months and 1 year after OLT demonstrated normal findings or a low-grade stenotic anastomosis of the hepatic artery and portal vein. Significant changes mainly occurred at the anastomotic site of the hepatic artery and were unpredictable.

Angiography still forms part of the protocol for evaluating children after OLT at our department. To investigate whether Doppler ultrasound is a reliable method for eva-
luating the patency of the hepatic artery, portal vein, inferior vena cava and the anas-
stomotic site of the portal vein in children after OLT, Chapter 5 describes a prospec-
tive study in which Doppler ultrasound was compared to angiography in 38 children
with 40 transplants (10 examinations on clinical demand and 49 examinations accor-
ding to protocol).

Good correlation was found in relation to demonstrating a patent hepatic artery (sensi-
tivity 96% and specificity 100%). Two false-negative Doppler ultrasound results were
attributable to technical difficulties and rejection. For evaluating the patency of the
portal vein, Doppler ultrasound agreed with angiography in 58 out of the 59 examina-
tions (98%). The one and only false-positive angiography result was explained by in-
adequate opacification. Doppler ultrasound visualized stenosis of the portal vein three
times more often than angiography. In seven children, Doppler ultrasound findings
suspicious of pathology of the inferior vena cava were confirmed using cavography or
surgery.

Doppler ultrasound proved to be a reliable technique for evaluating the patency of the
hepatic artery, inferior vena cava, portal vein and the anastomotic site of the portal
vein.

The value of ultrasound versus cholangiography for diagnosing generalized changes of
the bile ducts has not been investigated in a comparative study. The question arises as
to whether ultrasound can provide evidence to support the need for cholangiography in
the evaluation of graft dysfunction after OLT. In a study described in Chapter 6, we
investigated the ability of ultrasound to detect biliary obstruction, leakage and genera-
lized ductal changes. The findings were compared to those obtained with cholangio-
graphy.

Cholangiography was considered to be the gold standard. Adequate opacification of the
biliary tree was achieved in 139 cholangiograms. Biliary obstruction, intermediate or
large bile leakage and generalized ductal changes were diagnosed with cholangiogra-
phy in 15% (21/139), 14% (20/139) and 16% (22/139), respectively.

Normal ultrasound findings could not exclude biliary stricture, generalized ductal
changes, or bile leakage, while fluid collections were not correlated with bile leakage.
Abnormal ultrasound findings were highly predictive of the cholangiographic diagnosis
of biliary obstruction or generalized ductal changes (specificity of 98% and 100%,
respectively) and may, therefore, provide evidence to support the need for cholangi-
ography in the evaluation of graft dysfunction after OLT.

An irregular appearance of the bile ducts and increased periductal echogenicity proved
to be characteristic features for generalized ductal changes.

Chapter 7 deals with the question of whether serial Doppler ultrasound examinations
of the hepatic artery and hepatic vein are useful in the diagnosis of acute rejection.
To analyse changes in Doppler ultrasound variables in relation to liver biopsy findings
for the diagnosis of acute rejection after OLT, we performed 316 Doppler ultrasound
examinations prospectively on 23 patients in the first 2 weeks after OLT.

Recordings were obtained daily from the hepatic artery (resistive index = RI) and
hepatic vein (damping index = DI). Correlations were explored between the Doppler ultrasound findings and histological data. The chi-square test was used to analyse differences in Doppler ultrasound variables in patients with and without acute rejection.

Serial Doppler ultrasound examinations showed a significant increase in the RI in 11 out of the 22 patients (50%); the 23rd patient was excluded because of hepatic artery thrombosis. Despite agreement in 15 out of the 22 patients (68%), no statistically significant correlation could be found (positive predictive value 6/11 = 55%; negative predictive value 9/11 = 82%; chi-square = 3.14; P > 0.05). A significant increase in the DI was observed in 14 out of the 23 patients (61%). However, no statistically significant correlation could be found with this parameter (positive predictive value 6/14 = 43%; negative predictive value 6/9 = 67%; chi-square = 0.00; P > 0.05). Based on our results, serial Doppler ultrasound examinations of the hepatic artery and hepatic vein were not helpful in predicting acute rejection.

Loss of normal continuous flow, with the appearance of a dampened pulsatile flow in the portal vein, has been associated with acute rejection. Other investigators found that low velocity flow in the portal vein and prominent portal structures suggested rejection.

These observations were the reason for a prospective study to address the question of whether performing Doppler ultrasound routinely in the early postoperative period can help to evaluate rapid changes in portal hemodynamics in the case of acute rejection (Chapter 8).

To analyse changes in Doppler ultrasound variables of the portal vein in relation to liver biopsy findings, 316 Doppler ultrasound examinations were performed on 23 patients in the first 2 weeks after OLT. Recordings were obtained daily from the portal vein (diameter, maximum velocity and flow). Correlations were explored between the Doppler ultrasound findings and histological data. The chi-square test was used to analyse differences in Doppler ultrasound variables in patients with and without acute rejection. In our series of 23 patients, acute rejection was diagnosed by liver biopsy in nine of them (39%). Changes in portal vein diameter, maximum velocity and flow did not correlate consistently with liver biopsy findings, due to a multifactorial origin. Changes in portal hemodynamics were observed in patients with hepatic artery thrombosis, portal vein stenosis, acute rejection, and sepsis.

Although routine screening using Doppler ultrasound proved to be useful for the determination of rapid changes in portal hemodynamics, serial Doppler ultrasound examinations were not helpful in predicting acute rejection.
CONCLUSIONS

1. Doppler ultrasound and abdominal aortography are the starting points for pre-operative evaluation of the portal vein and hepatic artery in children who are candidates for OLT. Selective angiography is only useful if there is no conclusive information about the suitability of the portal vein or the hepatic artery.

2. Doppler ultrasound can replace cavography in pediatric OLT candidates. Cavography is only indicated when Doppler ultrasound demonstrates abnormal flow in the retrohepatic segment, or when the suprahepatic segment of the IVC and its junction with the right atrium cannot be identified.

3. It is not necessary to perform angiography routinely at discharge 2 months after OLT and at 1 year follow-up. In most patients, routine angiography demonstrated normal findings or a low-grade stenotic anastomosis of the hepatic artery and portal vein. Significant changes mainly occurred at the anastomotic site of the hepatic artery and were unpredictable.

4. Doppler ultrasound is the method of choice for evaluating the patency of the hepatic artery, portal vein, IVC and the anastomotic site of the portal vein in children after OLT. Angiography and cavography should only be performed if the Doppler ultrasound findings are inconclusive or indicate vascular complications in a child with symptoms of portal hypertension, ischemia of the liver, or the IVC syndrome.

5. Ultrasound cannot replace routine tube cholangiography or ERCP for the early detection of biliary stricture, bile leakage and generalized ductal changes. However, abnormal ultrasound findings have high predictive value for biliary obstruction or generalized ductal changes, and may, therefore, provide evidence to support the need for PTC or ERCP to evaluate graft dysfunction in the late postoperative period after tube removal.

6. Serial Doppler ultrasound examinations of the hepatic artery, hepatic vein and portal vein in the first 2 weeks after OLT (daily) do not contribute to predicting acute rejection.

Several considerations for the future

There is definitely a place for Doppler ultrasound in the screening of liver transplant candidates and in the evaluation of complications after OLT. The use of all available and different diagnostic modalities is too expensive and may be harmful for the patient. Over the past few years, considerable advances have been made in diagnostic imaging.
However, new sophisticated imaging techniques that have been introduced require cost-benefit-risk considerations.

- The combination of Doppler ultrasound and contrast-enhanced magnetic resonance angiography (CE-MRA) has been recommended for the screening of liver transplant candidates and will eliminate the need for angiography and cavography.

- The prognosis of acute liver failure and the success of OLT depend largely of the presence or absence of edema of the brain. Transcranial duplex Doppler ultrasound with a low frequency transducer can identify vascular structures and provide information on the flow state of the intracerebral vessels. Early diagnosis of edema of the brain by routine transcranial duplex Doppler ultrasound may contribute to improving the therapeutic results.

- Color Doppler ultrasound and the use of ultrasound contrast agents or Power Doppler ultrasound make it possible to distinguish low arterial flow from HAT. Consequently, unnecessary angiograms under general anesthesia in critically ill patients can probably be avoided in the future.

- Magnetic resonance cholangiography (MRC) does not require either contrast agent or biliary intervention and provides valuable information about the biliary system. It has the potential to reduce the number of invasive retrograde endoscopic cholangiographic examinations and may help in the planning of interventional procedures after OLT.

It is a challenge for the radiologist to find a logical sequence for the diagnostic imaging modalities that provide definitive and maximum information and are safe, painless and well-tolerated by the patient before and after OLT: *when life depends on the liver.*