Cost and outcome of liver transplantation

van der Hilst, Christian

Chapter 8

Implantable Continuous Doppler Monitoring Device for Detection of Hepatic Artery Thrombosis after Liver Transplantation

Koert P. de Jong
Jasper Bekker
Stijn van Laarhoven
Sven Ploem
Patrick F. van Rheenen
Marcel J.I.J. Albers
Christian S. van der Hilst
Henk Groen

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ABSTRACT

Background. Early hepatic artery thrombosis (eHAT) after liver transplantation occurs in 3% of adults and 8% of children and often results in retransplantation. eHAT is initially asymptomatic and arterial patency is monitored with percutaneous Doppler ultrasound screening (pDUS). The aim of the study is to analyze the diagnostic accuracy of 'CONtinuous' DOppler Registration (CONDOR) using an implantable miniature Doppler.

Methods. This prospective observational study was conducted in 102 liver transplant recipients. Hepatic arterial signal is checked by CONDOR at least six times per day for the first 10 days after transplantation with comparison of diagnostic accuracy of CONDOR versus pDUS. An economic evaluation was carried out by comparing pDUS and CONDOR.

Results. Extra investigations were performed after 48 (11%) regular pDUS where arterial patency was questioned: 32 extra pDUS, 14 computed tomography (CT) angiographies, and 2 reoperations. CT scan confirmed eHAT in 4 cases. In 10 cases of pDUS-suspected eHAT, where subsequent CT showed an open artery, the CONDOR signal was clearly pulsatile. In 2 of 4 patients with five eHATs, a weak arterial signal was inadvertently interpreted as an open artery (sensitivity of 60%). The accuracy for detection of eHAT increased from 93% (pDUS) to 99% (CONDOR). Using CONDOR, additional CT angiographies may be prevented in 10% of cases. Mean cost per patient for pDUS were € 392 while CONDOR had mean costs of € 677 for the 10-day monitoring period.

Conclusion. CONDOR is a useful adjunct to pDUS because it reduces the false-positive rate of pDUS. Further development of the technique and analysis of the signal generated by CONDOR are needed to improve the sensitivity before CONDOR can replace pDUS as a reliable screening method for detection of eHAT. The additional costs for CONDOR are limited.

1 INTRODUCTION

Liver transplantation is the only life-saving treatment for patients with end-stage liver disease. Early hepatic artery thrombosis (eHAT) is a serious complication that occurs in 3% of adults and up to 8% in children[1]. Approximately 30% of early retransplantations are caused by HAT[2,3]. Retransplantation is associated with extra morbidity and mortality and is a burden to the shortage of suitable donor organs[4,5]. Early detection of eHAT with instantaneous attempts for revascularization may avoid retransplantation[6,7]. Because eHAT is asymptomatic, it can only be detected by screening, which is performed by percutaneous Doppler ultrasound screening (pDUS). In the case of suspected eHAT CT [computed tomography] angiography serves as reference standard. The assessment of the arterial supply to the liver graft using pDUS is difficult in the presence of obesity, interposed gas, or prominent portal blood flow. For these reasons, pDUS can be associated with false-positive results[8,9]. Additionally, the intermittent character of pDUS can cause a considerable delay in the diagnosis of eHAT. Continuous monitoring of arterial flow would shorten the time between the thrombotic event and the surgical intervention.

In the present study, a miniature implantable Doppler ultrasound probe was fixed to the hepatic artery at the end of the transplantation and the patency of the hepatic artery was checked by CONtinuous DOppler Registration (CONDOR). The primary objective was to assess the accuracy of CONDOR in comparison with standard pDUS. The secondary objective was to compare the cost of CONDOR monitoring with standard pDUS.

2 MATERIALS AND METHODS

2.1 Study design and participants

The study protocol was approved by the Medical Ethics Committee of the University Medical Center Groningen (number 06.033). Informed consent was obtained from patients, parents of pediatric patients, or formal representatives in subconscious/encephalopathic patients referred for liver transplantation. The study was registered at the site of the Netherlands Organization for Health Research and Development [*http://www.zonmw.nl/nl/projecten/project-detail/continuous-flow-registration-for-early-detection-of-hepatic-artery-thrombosis-after-liver-transplan/samenvatting/*] and was reported according to the standards for the reporting of diagnostic accuracy studies (STARD) recommendations.

In this prospective observational study with invasive measurements on liver transplant patients, the commercially available Cook-Swartz Doppler Flow Probe/Blood Flow Monitor system was used for continuous Doppler flow measurement (Cook Medical, Limerick, Ireland). The sterile probe consists of a 20 MHz Doppler crystal mounted on the inside of a semicircular silicone cuff (Figure 1). The cuff is fixed around the donor hepatic artery with a Vicryl-Rapide 5-0 resorbable suture (Ethicon, Johnson & Johnson, Amersfoort, the Netherlands) without constricting the artery (Figure 2). Rapid resorption of this suture prevents the development of a circular stricture around the artery, which is especially important in children because of ensuing growth. The connection wire is exteriorized through the wound.

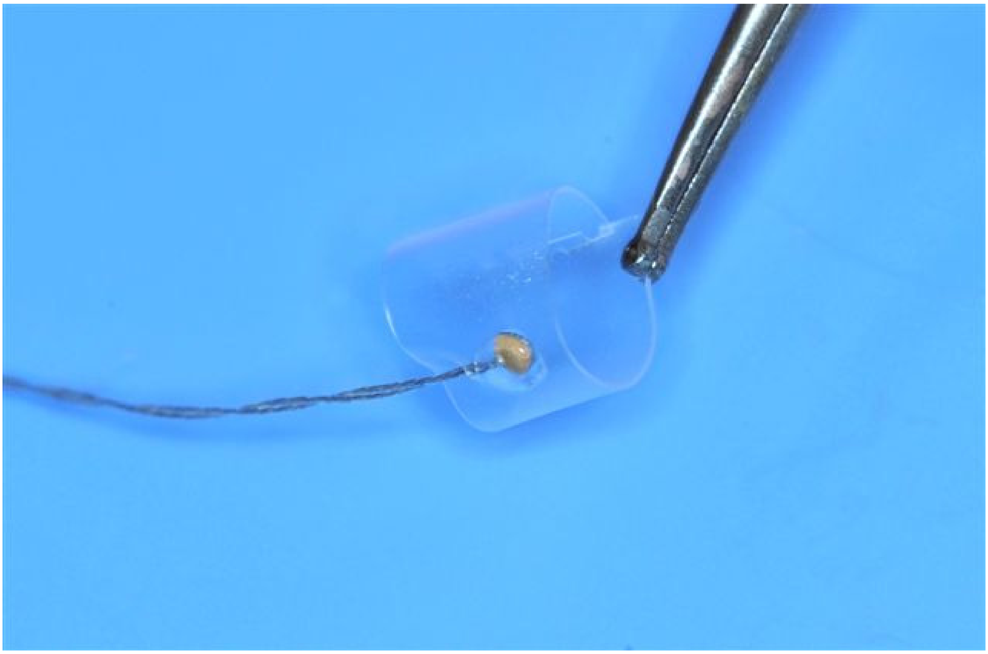

Figure 1. Doppler crystal mounted on the semicircular silicone cuff.

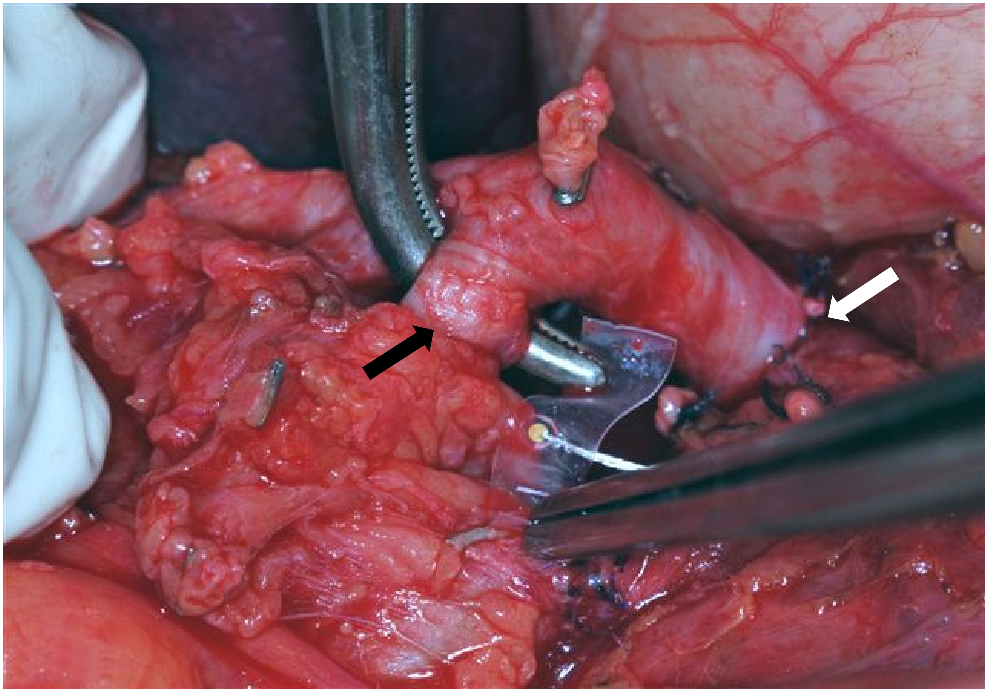

Figure 2. Intraoperative view of implantable Doppler device which is applied to the right hepatic artery of the donor liver (black arrow). Arterial anastomosis (white arrow) between donor and recipient hepatic artery.

The hepatic arterial pulsatile signal was checked by trained personnel every 2 hours on the intensive care unit and every 6 hours on the ward. An example of a recorded audible arterial signal is available online. The soundtrack available online [http://links.lww.com/TP/A711] is an example of a pulsatile audible signal generated by the Cook Vascular Blood Flow Monitor of a hepatic artery of a transplanted liver. According to the protocol, pDUS was performed once daily on days 1, 2, 3, 4, 7, and 10 in children and days 1, 4, and 7 in adults. We consider the higher number of pDUS in children rational because of the higher risk of eHAT in children. pDUS was performed in a blinded way, with the radiologist unaware of the results of the CONDOR. The time used for performing pDUS was recorded. In case of undetectable flow, a highly experienced radiologist was called in to perform an extra pDUS. If a pulsatile arterial signal was not detectable with the CONDOR, technical problems were excluded by checking cables and monitor according to the manufacturers' instructions. If no technical failure could be detected, the radiologist performed an immediate extra pDUS. If no arterial signal was detectable during the extra pDUS examinations, either the extra pDUS by the experienced radiologist or the extra pDUS when the CONDOR signal was not present, a contrast-enhanced multiphase CT scan was performed. If eHAT was confirmed, the patient was taken to the operating room for a revascularization procedure. If either the radiologist or the CT angiography clearly demonstrated a patent artery but the pulsatile signal of the CONDOR probe remained absent, the probe was removed after 24 hours. If the pulsatile signal returned, the probe was left in for further monitoring, but the event was scored as a false-positive registration. At day 10 after transplantation, the CONDOR probe was removed on the ward.

2.2 Economic evaluation

Two scenarios were analyzed for the economic evaluation. The first scenario is based on the addition of CONDOR to the current routine pDUS examinations. The second scenario is based on the assumption that, based on future refinement of the device, the accuracy of CONDOR is so high that it can replace routine pDUS examinations, except for a baseline day 1 Doppler ultrasound. The baseline pDUS will give information not only of the arterial blood flow but also about the portal vein, hepatic veins, texture of the liver parenchyma, and the bile ducts. In the second scenario, the other routine pDUS examinations can be eliminated.

The economic evaluation was performed as a cost-consequence analysis, comparing costs and effects of standard pDUS with that of the CONDOR. Only direct medical costs of procedures applicable to both situations in the study period of 10 days were included. The price level for 2009 was used; prices of previous years were adjusted by indexing based on the consumer price index [http://www.cbs.nl].

The costs of CONDOR consisted of the purchase price of the equipment (monitor € 3050 and reusable cable € 103) and the disposable Doppler probe (€ 460). The costs related to additional operating time (7 min at most) and suture material were considered negligible. Equipment annual depreciation rate was set at 20%, and the number of monitors needed for our center with 60 transplants per year was set at 5.

The costs of pDUS (€ 74.68) and CT angiography (€ 239.34) were based on 'College Tarieven Gezondheidszorg' tariffs. The costs of time investment for the pDUS were based on Dutch standard costs for medical specialist (€ 107.50/hour)[10]. The costs of relaparotomy and urgent retransplantation were based on data from the Dutch multicenter COLT-study and were € 2500 and € 46 253, respectively. The potential savings when using the CONDOR probe consist of savings of routine pDUS examinations and the required extra investigations because of suspicion of eHAT on routine pDUS examination.

2.3 Data analysis

Sensitivity, specificity, positive and negative predictive values, and 95% confidence intervals were calculated. Accuracy of the two diagnostic strategies (CONDOR and pDUS) was compared. The J value as a measure of agreement was calculated between CONDOR and pDUS.

3 RESULTS

3.1 Clinical evaluation

The first patient was included in January 2008. In total, 102 patients (23 children and 79 adults) were included in the study. In 18 patients, two probes were implanted on two separate donor arteries supplying the transplanted liver. Table 1 presents the clinicopathologic characteristics.

Table 1. Demographic data of the study population.

Variable	Children n/n, median (range)	Adults n/n, median (range)
Number of patients	23	79
Male/female	12/11	49/30
Age (years)	3.1 (0.3 - 14.5)	57.7 (18 - 68)
Diagnosis		
biliary atresia	10	1
cholestatic disease	6	14
acute hepatic failure	4	8
metabolic disease	3	7
NASH	0	9
alcoholic cirrhosis	0	10
viral cirrhosis	0	7
cryptogenic cirrhosis	0	6
various	0	17

Table 1. Demographic data of the study population (continued).

Variable	Children n/n, median (range)	Adults n/n, median (range)
Type of graft		
full size, heartbeating	5	56
full size, non-heartbeating	0	21
reduced	6	0
split	8	2
living related	4	0
First/retransplantation	19/4	64/15
Implanted CONDOR probes 1/2	21/2	63/16
ICU stay (days)	7.5 (3 - 34)	3.0 (1 - 34)

Abbreviations: *NASH = nonalcoholic steatohepatitis; CONDOR = 'continuous' doppler registration, ICU = intensive care unit.*

In four patients, five instances of eHAT were diagnosed. In three patients, eHAT occurred on day 1, and in one patient, two eHAT events occurred on days 4 and 10. Three of the five events were correctly diagnosed by CONDOR. One patient had a reconstructed right hepatic artery and received two CONDOR probes separately on the right and left hepatic arteries. The CONDOR signal of the right hepatic artery disappeared on day 1 and eHAT was confirmed on CT angiography, which showed supply of the right liver lobe via the left hepatic artery. Revascularization was not considered necessary and the patient recovered uneventfully. This event was characterized as true positive. The other patient with an immediate detection of absent hepatic arterial flow was a 6-month-old child with acute liver failure, who received a reduced segment 2,3 graft. On day 4, the CONDOR signal disappeared and the absence of flow in the hepatic artery was confirmed by an urgent additional pDUS and CT angiography. An immediate revascularization was performed, which was initially successful. On day 10, the CONDOR again suggested eHAT and an immediate relaparotomy were performed, which revealed dilated bowel and mechanical obstruction of the hepatic artery. The abdomen was temporarily closed using a silastic patch to create decompression. The final outcome was uneventful. In the other two patients with eHAT, the CONDOR signal at day 1 was still present but weaker than the previous registrations. On pDUS and CT angiography, eHAT was diagnosed. Both patients underwent operative revascularization, which was successful in one patient. The other patient underwent retransplantation because of persistent biliary problems despite an open hepatic artery. Table 2 presents the data on routine and extra investigations separately for children and adults.

Table 2. Number of routine investigations, time investment, and additional investigations in patient population.

Variable	Children (n = 23)	Adults (n = 79)	*p*-value
Number of pDUS	170	266	
per patient			< 0.001
mean (SD)	7.4 (1.7)	3.4 (0.9)	
median (range)	7.0 (2 - 10)	3.0 (1 - 8)	
Total time investment of pDUS (min)	3005	7220	
per patient			0.005
median (IQR)	123 (88)	86 (51)	
range	21 - 248	28 - 193	
per pDUS			< 0.001
median (IQR)	16.9 (9.7)	27.7 (15.0)	
range	2.6 – 33.0	9.3 - 71.5	
Àdditional investigations (number)	8	40	
pDUS[a]	5	27	
CT angiography[b]	1	13	
laparotomy[c]	2	0	

[a] Including the four cases in whom the extra pDUS was performed because of a false-positive CONDOR signal. [b] Including the four patients in whom eHAT was found. [c] Consisting of the two immediate laparotomies performed because of suspicion of eHAT based on absent flow on CONDOR and pDUS (n = 1, occluded artery) and absent flow on pDUS but normal flow on CONDOR (n = 1, open artery). In these two cases, preoperative confirmation by CT angiography was not performed. ***Abbreviations:*** *pDUS = percutaneous doppler ultrasound screening, SD = standard deviation, min = minutes, IQR = interquartile range, CT = computed tomography.*

On a per-patient basis, the pDUS in adults was more time-consuming than in children. The number of extra pDUS examinations was 32 in 28 patients. On 28 occasions (6.4% of 436 pDUS), this was because regular pDUS did not reveal an arterial signal. In only one patient, eHAT was diagnosed and treated by a successful revascularization, whereas the other 27 extra pDUS examinations (6.2%) were performed in patients with a normal pulsatile CONDOR signal and patent hepatic arteries as confirmed by extra pDUS. On four occasions, the CONDOR probe suggested an eHAT that was not confirmed by additional pDUS examinations. These were the only extra investigations initiated by false-positive CONDOR findings. In one patient, the signal did not recur, whereas in three patients the pulsatile signal recurred within 24 hour and the probes were left in and functioned normally afterward. All these four events were scored as false-positive events for CONDOR. On 14 occasions in 12 patients, CT angiographies were performed because of a high suspicion of eHAT based on pDUS. These included the four patients with a proven eHAT, whereas the other 10 CT angiographies were performed in eight patients with a normal pulsatile CONDOR signal in whom patency of the hepatic artery was confirmed on CT. In total, 37 extra investigations were performed for suspected eHAT in the presence of a normal CONDOR signal; this represents 8.4% of the 436 routine pDUS.

In the 23 children, 170 pDUS events were performed. In one child, no arterial signal could be detected on pDUS despite a normal arterial CONDOR signal.In this patient, after a living related transplantation, an immediate laparotomy, without confirmation by CT angiography, was performed and a patent artery was found and the case was characterized as false positive for pDUS and true negative for CONDOR.

The accuracy of the diagnostic test increased from 93% with pDUS to 99% with CONDOR (Tables 3 and 4).

Table 3. Relation between the results of CONDOR and the presence of eHAT.

	Presence or absence of eHAT		
CONDOR	**eHAT (+)**	**No eHAT(-)**	**Total**
eHAT (+)	3	4	7
No eHAT(-)	2	427	429
Total	**5**	**431**	**436**

Measures	**%/ n**	**95% confidence interval**
Sensitivity	60% (3/5)	23.1% - 88.2%
Specificity	99.1% (427/431)	97.6% - 99.6%
Positive predictive value	42.9% (3/7)	15.8% - 75.0%
Negative predictive value	99.5% (427/429)	98.3% - 99.9%
Accuracy	98.6% (422/428)	
Positive likelihood ratio	64.65	19.28 - 216.76
Negative likelihood ratio	0.40	0.138 - 1.181

Abbreviations: *eHAT = early hepatic artery thrombosis, CONDOR = continuous doppler registration.*

Table 4. Relation between the results of pDUS and the presence of eHAT.

	Presence or absence of eHAT		
pDUS screening	**eHAT (+)**	**No eHAT (-)**	**Total**
eHAT (+)	5	31	36
No eHAT(-)	0	400	400
Total	**5**	**431**	**436**

Measures	**%/ n**	**95% confidence interval**
Sensitivity	1.0 (5/5)	0.565 - 1.0
Specificity	0.928 (400/431)	0.9 - 0.949
Positive predictive value	0.139 (5/36)	0.061 - 0.287
Negative predictive value	1.0 (400/400)	0.99 - 1.0
Accuracy	0.929 (405/436)	
Positive likelihood ratio	13.9	9.9 - 19.52
Negative likelihood ratio	-	-

Abbreviations: *eHAT = early hepatic artery thrombosis, pDUS = percutaneous doppler ultrasound screening.*

This increase in accuracy is mainly caused by the high incidence of undetectable arterial signals with routine pDUS, suggestive of eHAT, in which eHAT was absent on extra investigations (false positives for pDUS). On 36 occasions, pDUS did not detect an arterial signal. On 31 occasions, this was a false-positive result, and on the other five occasions, a correct diagnosis of eHAT was made (pDUS sensitivity of 100%). The sensitivity of CONDOR is 60%, which is caused by missing two of the five cases of eHAT. The agreement between pDUS and CONDOR was poor, with a J value of 0.137 (95% confidence interval, -0.011 to 0.285).

Removal of the CONDOR probe at the end of the study period was without complications. We did not encounter bleeding or infectious complications, which were likely or possibly related to the CONDOR probe. There was no 30-day mortality, except for one 54-year-old patient transplanted for hepatitis C and alcohol-related liver disease, who died at day 3 after transplantation because of progressive pulmonary failure related to severe portopulmonary hypertension.

3.2 Economic evaluation

The costs of use of the CONDOR monitor were calculated at € 52.55 per patient. The costs of the probes were based on the actual number of 120 probes used in the study. Because the sensitivity of CONDOR is not sufficiently high, it cannot replace pDUS investigations. Thus, the economic evaluation of the first scenario consists of the costs of the simultaneous use of CONDOR and pDUS. This combines the high sensitivity of pDUS and the high specificity of CONDOR and is associated with extra costs of € 544 per patient for the 10-day period. If future studies reveal that also a high sensitivity of CONDOR can be obtained (see Discussion), CONDOR can replace the majority of pDUS investigations in the posttransplantation period. In this second scenario, we advocate a routine pDUS only on day 1, as a baseline investigation of the transplanted liver, with CONDOR replacing pDUS monitoring for the rest of the postoperative period. This scenario would result in elimination of 334 routine pDUS examinations in 102 patients (total cost savings of € 24 943), 28 extra pDUS examinations for presumed eHAT (total cost savings of € 2091), cost savings of prevented CT angiographies (€ 2393), and cost savings of the relaparotomy for presumed eHAT (€ 2500). Based on these numbers, the total savings, by eliminating the extra investigations and procedures, are € 31 927 or € 313 per patient. With this scenario, the costs associated with CONDOR are € 286 per patient for the 10-day monitoring period (Table 5).

The costs of use of the CONDOR registration were calculated based on the purchase price of the equipment (€ 3050 for the monitor and € 103 for the reusable cable) and disposable materials (€ 460 for the Doppler probe). A prerequisite for CONDOR replacing conventional pDUS is that sensitivity should be near 100%. Only then can CONDOR be considered sufficiently reliable. Additional costs of CONDOR per patient are € 677 - € 392 = € 286 for the 10-day monitoring period.

Table 5. Cost analysis of conventional pDUS and CONDOR.

	pDUS		CONDOR	
Cost category	**n**	**€**	**n**	**€**
regular pDUS (€ 74.68/ measurement)	436	32 560	102[a]	7617
of which: personnel		*11 991*		*2805*
of which: materials and overhead		*20 572*		*4813*
Time personnel regular pDUS	10 225	17 924	2689[a]	4797
CONDOR monitor (€ 52.55/ patient)	-	0	1	5308
CONDOR probes	-	0	120	55 200
Extra investigations[b]				
pDUS	28	2091	4	299
CT angiography	10	2393	-	0
laparotomy	1	2500	-	0
Total costs		**39 547**		**68 424**
Cost per patient		**392**		**677**

[a] CONDOR group includes one regular pDus at day 1. [b] Based only on extra investigations in patients in whom the diagnosis of eHAT was presumed but could not be confirmed. ***Abbreviations:*** *CONDOR = continuous doppler registration, pDUS = percutaneous doppler ultrasound screening, CT = computed tomography.*

4 DISCUSSION

The application of CONDOR of the hepatic artery after liver transplantation increased the accuracy of a diagnosis on the patency of the hepatic artery from 93% for intermittent pDUS by the radiologist to 99%. This high accuracy is mainly caused by an excellent low false-positive rate of the CONDOR. However, the sensitivity is not sufficiently high (60%) because CONDOR missed two of five instances of eHAT. Although, in both missed cases, the CONDOR signal was less clear than before, this was inadvertently interpreted as an open artery. During relaparotomy, we found that the Doppler crystal on the donor hepatic artery was positioned too close to the arterial anastomosis and was probably picking up the nonflowing but still pulsating column of blood in the recipient hepatic artery close to the anastomosis. To prevent this, we advocate that the crystal should be placed on the donor artery as close to the liver as possible. Another reason could be that the CONDOR monitor only generates an audible signal that is not quantifiable. Improvement of the system is needed with the aim to generate and store visible and quantifiable pulse characteristics, such as resistive index, systolic acceleration time or peak systolic velocity, and the possibility to generate alarm signals if certain predetermined limits are exceeded.

A reliable continuous monitoring of the hepatic artery could prevent the side effects of additional examinations. The disadvantages of CT scanning are predominantly associated with radiation exposure and side effects of iodinated contrast agents[11-13]. Radiation dosage is among the highest in CT angiography[14]. Especially with respect to the radiation-induced cancer risk, the consequences of exposure to radiation are increasingly recognized[15,16]. Radiation exposure should be minimized in transplant patients because of the already increased risk of developing cancer attributable to lifelong immunosuppression[17, 18]. Similarly, the nephrotoxicity of contrast agents adds to that of calcineurin inhibitorYbased immunosuppression[19-21]. The incidence of chronic renal failure within five years after transplantation of a nonrenal organ varies from 7% to 21%, with liver transplant patients being among those with the highest incidence[22]. Moreover, many cirrhotic patients already have renal function disturbances[23].

On four occasions, we obtained false-positive CONDOR results, necessitating the only four extra examinations initiated by CONDOR. Remarkably, in three cases, the signal recurred several hours later, suggesting a temporarily insufficient contact between the ultrasound crystal and the arterial wall. In one child, the CONDOR probe became disconnected on day 3, which was very likely associated with substantial distention of the abdomen due to ascites and paralytic ileus. Sufficient surplus of length of the CONDOR cable between the artery and the abdominal wall should be left in the abdomen to prevent this complication. Another important lesson from this study was obtained from the two patients with eHAT in whom the CONDOR signal was still detectable. In both cases, the pulsatile signal was less clear, and in one patient, diastolic flow was not detectable. Relaparotomy in these patients suggested application of the CONDOR probe too close to the end-to-side arterial anastomosis of the donor artery to the recipient proper hepatic artery. Despite the absence of flow in the hepatic artery, we assume the CONDOR probe picked up slight movements of the pulsating column of blood adjacent to the anastomosis with a further downstream occlusion. These two false-negative events are the cause of the sensitivity of 60% of the CONDOR strategy. To prevent false-negative CONDOR results, we advocate a further downstream placement of the CONDOR probe on the donor hepatic artery.

The economic evaluation needs some clarification. It is clear that CONDOR first needs a higher sensitivity before it can replace the routine pDUS examinations. Provided that this can be obtained, the use of CONDOR still is associated with some extra costs. The main reason for this is the low tariff for pDUS; elimination of the many routine pDUS examinations will thus not lead to a significant reduction in costs. Nevertheless, for € 28.60 per day, continuous monitoring of the hepatic artery is guaranteed by CONDOR, which is reassuring for both the patient and the physician. This is, in our opinion, a low price because the occurrence of eHAT can be disastrous and it is likely that early diagnosis and an immediate revascularization attempt can possibly prevent a retransplantation. Costs associated with an urgent retransplantation can mount up to € 46 253. These costs can be variable because they do not include only the costs of the transplantation itself but also costs of airborne transportation of the donor liver.

The potential advantages of CONDOR are more pronounced if the incidence of eHAT is high because positive and negative predictive values depend on the incidence of the event under study. In a systematic review, we reported that the eHAT incidence is higher in low-volume centers and in centers with an active pediatric transplant program[1]. Therefore, centers with a high eHAT incidence will benefit more from CONDOR monitoring than centers with a low incidence. In the same systematic review, we found that 96% of transplantation centers perform pDUS with a frequency range from twice daily to once daily in 3 days. We did not encounter articles reporting on continuous monitoring of eHAT.

Although continuous monitoring of hepatic arterial flow has been described earlier in small patient series[24,25], this is the first study comparing continuous monitoring with routine screening pDUS in a standardized protocol manner. We conclude that continuous monitoring of hepatic arterial blood flow after liver transplantation might be the way to go because it is the only way to detect eHAT as soon as possible. This offers the best chances for an early revascularization and prevention of a retransplantation. This study reveals that further evolution of continuous Doppler monitoring is necessary, especially to improve the sensitivity of the device. We are exploring this further development. Continuous monitoring of a time event, such as vascular thrombosis, will probably contribute to earlier diagnosis and intervention. This will hopefully lead to a reduced loss of transplanted organs, probably not only livers but also other organs, which is essential regarding the scarcity of donor organs.

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