Hepatobiliary Scintigraphy in a Pediatric Population: Determination of Hepatic Extraction Fraction by Deconvolution Analysis

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A study was performed to assess the feasibility of measuring the hepatic extraction fraction (HEF) and hepatic half clearance time (HCT) in pediatric patients with a variety of hepatobiliary diseases. There were 45 children categorized into four groups: normal 12; obstruction 9; hepatocellular disease (HCD) 16 and miscellaneous 8. In the normal patients, the mean HEF was 99% ± 3.6% and the HCT was 23.6 ± 7.7 min. In the two disease categories, hepatocellular disease and obstruction, there was a wide range of HEF 15%–84% and 25%–100%, respectively. This reflected the varying degrees of liver dysfunction and/or cholestasis. The average results of HEF for the HCD group was significantly lower than controls, and the greatest difference of the HCD group and other disease groups was with the miscellaneous group. This was not, however, different from the obstructive group. There was, however, a large overlap of results, and differentiation between the disease groups was not possible. HCT from the disease groups also showed a prolonged average clearance when compared to normals, although this was not significant when the p value was adjusted for multiple comparisons. The normal HCT was 23.6 ± 7.7 min, whereas the hepatobiliary disease groups ranged from 20 to 714 min. Again, there was considerable overlap of results in the disease groups. These functional parameters are feasible and applicable in the pediatric population.

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Since the introduction of ^{99m}Tc-iminodiacetic acid (IDA) compounds, hepatobiliary imaging has become widely accepted for use in both adult and pediatric patients (*1–3*). The differentiation of primarily biliary from hepatocyte disease by hepatobiliary scintigraphy may be difficult. The image patterns generally are different between the two groups. In biliary disease, before compromise of hepatocyte function occurs, the hepatobiliary agents are extracted rapidly and excreted into bile. This occurs to varying degrees depending on the level and degree of obstruction. In hepatocellular disease, there is delayed clearance from the blood pool, decreased extraction and persistent parenchymal uptake and delayed excretion into the gastrointestinal tract. There is, however, an overlap between these groups and the use of deconvolution analysis to measure hepatic extraction fraction (HEF) as a quantitative measure of hepatocyte function, and hepatic half clearance times (HCT) has been shown to be a valuable adjunct to hepatobiliary images in adults (*4,5*). However, to date these analyses have not been reported in children. We reviewed hepatobiliary scans in children to:

1. Establish normal HEF and HCT values in pediatric patients.
2. Determine whether HEF and/or HCT can differentiate hepatocellular disease from biliary disease.
3. Determine specific technical problems with these techniques in children.

MATERIALS AND METHODS

Hepatobiliary scans (HBS) of 45 children were reviewed for hepatocyte function and ^{99m}Tc-IDA clearance. There were 25 males and 20 females, ranging in age from 1 wk to 14 yr with a mean of 4.4 yr. The final diagnosis was obtained by clinical findings, biochemistry, radiology, nuclear medicine studies, pathology and surgery. The patients were divided into four categories based on their final diagnosis:

1. Normal. Scintigraphy was performed to investigate abdominal pain. Liver function tests (LFTs) were normal.
2. Biliary Tract Obstruction. The patients included four with biliary atresia, one with choledochal cyst, one with common duct stone with obstruction, one with acute obstruction post-liver transplant and two patients with syndromatic bile duct hypoplasia (Alagille's syndrome). All patients were jaundiced.
3. Hepatocellular Disease. Eight patients had neonatal hepatitis, three had hepatitis and five had cirrhosis. The diagnosis was confirmed on liver biopsy. All patients had abnormal LFTs and were jaundiced.
4. Miscellaneous. This group of patients was not jaundiced and included four patients with hepatomegaly, two with post-biliary surgery and one with a nonfunctioning gallbladder. They had normal LFTs except for mildly elevated LFTs

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in one patient with hepatomegaly and one patient with a nonfunctioning gallbladder.

Hepatobiliary Scintigraphy

All subjects were fasted for 3 hr. Technetium-99m-diisopropyl iminodiacetic acid (DISIDA) was given intravenously in a dose of 40–120 MBq according to body weight. The patients were scanned supine under a gamma camera and analog images were obtained at 1 frame per 3 sec for 60 sec, followed by 1 frame per 2 min for 60 min with simultaneous computer acquisition. Over the period of the study, two computer systems were used: Digital PDP 11/34 (DEC) and General Electric Starcam. Acquisition on the DEC consisted of 3 frame rates (1 frame per sec for 60 sec; 1 frame per 10 sec for 18 frames; 1 frame per 120 sec for 28 frames) and this was collected in 64 × 64 word mode. The Starcam acquisition included 2 frame rates (1 frame per 3 sec for 20 min and 1 frame per 60 sec for 60 frames) and was collected in a 128 × 128 word mode. The data were reframed to 1 frame per min for 60 min and deconvolution analysis was performed using the Fourier transform method (*4,5*). A region of interest (ROI) was drawn over the left ventricle of the heart, excluding the aorta and any scatter from the liver. A second ROI was drawn over the right upper lobe of the liver, excluding the gallbladder and any major hepatic ducts that may be visualized later in the study as well as any scatter from the heart. Time-activity curves were generated from these regions, and the heart curve was used as the input function and the liver curve as the output function for deconvolution analysis. Both these curves had a raised cosine function, as described by Juni (*5,6*), appended to their tails, therefore gradually tapering the curves to zero.

The Fourier transforms of both curves were determined, and the organ of interest curve was divided by the blood-pool curve in frequency space. A reverse Fourier transform was then performed and the resultant deconvolved liver curve is a hypothetical true liver response representing a direct bolus injection into the hepatic artery. An exponential curve of best fit was applied to the deconvolved liver curve, working backwards from the zero x-axis crossing point to the first frame that deviates from the exponential feature. This curve of best fit will cross the y-axis at a point proportional to hepatocyte function and is used in the final HEF equation, i.e.,

$$\text{HEF} = \frac{\text{y-intercept exponential fit liver response curve}}{\text{y max data value liver response curve}}.$$

The initial liver region time-activity curve was also generated for the determination of liver half clearance time (HCT). An exponential curve of best fit was applied to this curve and the half clearance time (HCT) was calculated using the equation: $T_{1/2} = -0.69$ divided by slope of the curve. The first point of the curve fit was subjectively placed at the maximum point prior to the excretion decrease and the best fit applied to the excretion curve.

The hepatobiliary scans were analyzed by two of the authors (RHG, RFU) and the imaging patterns were classified as follows:

1. Normal. Scintigraphy showed a rapid extraction and excretion of tracer into the biliary system by 8–12 min and visualization of the gallbladder and gastrointestinal tract by 1 hr. There was occasional prominance of the left hepatic duct in older patients but not usually in preadolescent patients (Fig. 1).
2. Biliary Tract Obstruction. Various patterns were seen in obstruction.
   a. Biliary Atresia. There was usually good extraction of tracer but no excretion seen into the gastrointestinal tract over a 24-hr period. There was a persisting parenchymal phase and no accumulation of tracer into bile ducts or gallbladder (Fig. 2).
   b. Obstruction to Common Bile Duct. Acute obstruction was diagnosed when there was good extraction of tracer and no excretion into the biliary tree in patients who had evidence of previous patency of the biliary system. Partial obstruction was reported if there was patency of the biliary system demonstrated, however, there was evidence of dilatation of the biliary tree and delayed clearance into the gastrointestinal tract (*7*).
   c. Choledochal Cyst. This diagnosis was reported if there was marked dilatation of the common bile duct and or cystic duct in conjunction with other imaging evidence of dilatation e.g., ultrasound, cholangiography.
3. Hepatocellular Disease. This was diagnosed when there was delayed blood-pool clearance of tracer with parenchymal retention of tracer and delayed excretion into the gastrointestinal tract. In some patients, the gallbladder may not be visualized (Fig. 3).
4. Miscellaneous. If the scan patterns did not correspond to the above patterns they were classified as this group (e.g., nonfunctioning gallbladder or hepatomegaly) (Fig. 4).

Statistics

Results are presented as mean ± standard deviation (s.d.) and analysis was performed using the unpaired Students t-test. Results were considered to be significant if the p value was <0.05. As multiple simultaneous comparisons were performed, this increases the chance of a significant result. A conservative adjustment was therefore obtained by multiplying the observed p value by the number of comparisons as described by Needleman et al. (*8*). A significant adjusted p value was <0.05.

RESULTS

The average values and s.d. for each hepatobiliary disease group and normal controls are seen in the Table 1. The p value was adjusted as described by Needleman et al. (*8*) because multiple simultaneous comparisons were made. In all disease categories, the average HEF was significantly lower than the controls and not unexpectedly the greatest difference was in the hepatocellular disease category ($p < 0.001$). Hepatocellular disease values were significantly lower ($p < 0.01$) than obstructive disease, but because of the gross overlap of values we could not discriminate between the two disease groups.

The ranges of HEF according to each category are illustrated in Figure 5. In normal children, the HEF varied from 87% to 100% and the average value was 99% ± 3.6%. The statistical lower limit of normal at 2 s.d. below the mean is shown by the solid line at a HEF of 92%. Of note, 11 of the 12 normal controls had a HEF of 100%. In contrast, only 7 (21%) of those in the disease categories (3 miscellaneous, 4 obstruction) had a HEF within the statistically normal range and 5 of the 7 were noncholes-

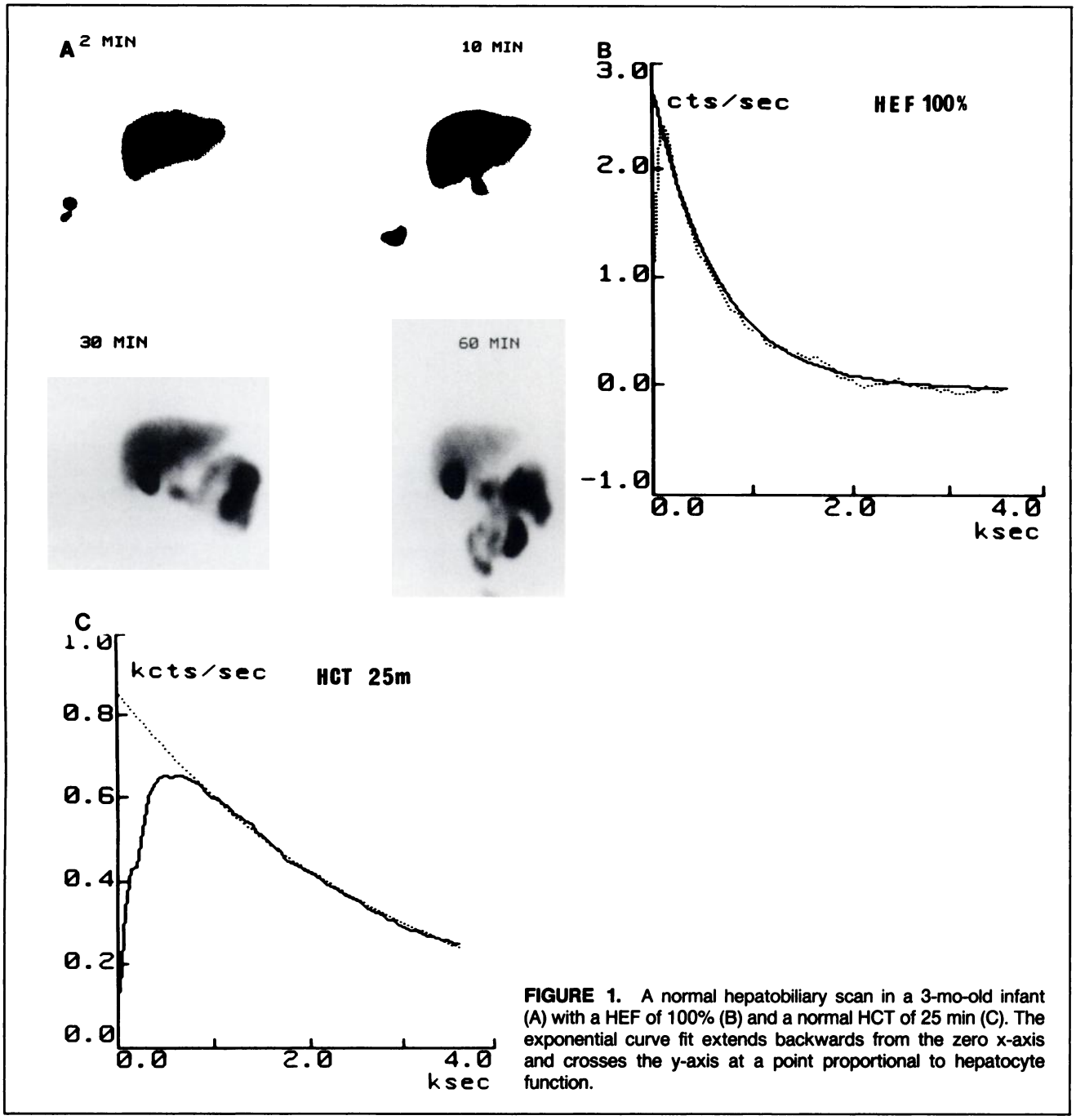

FIGURE 1. A normal hepatobiliary scan in a 3-mo-old infant (A) with a HEF of 100% (B) and a normal HCT of 25 min (C). The exponential curve fit extends backwards from the zero x-axis and crosses the y-axis at a point proportional to hepatocyte function.

tatic. No hepatocellular disease patients were within the statistically normal range. In both the hepatocellular disease and obstruction groups, there was a wide range of HEF, 15%–84% and 25%–100%, respectively. This presumably reflects the varying degree of liver dysfunction and/or cholestasis in these groups.

The average HCT values are also shown in the Table 1. Clearance times were significantly slower in the hepatocellular and obstruction groups but not in the miscellaneous group. The ranges of HCT are shown for the disease categories in Figure 6. Again, there was a significant prolongation of average clearance time in all three liver disease groups, with none of those with obstructive disease having a normal value. However, within the three disease categories, there was considerable overlap of results, and there was no discrimination between the obstructive and hepatocellular disease categories.

The major technical problems found in performing this analysis in infants and children were patient movement and the injection technique. Because ROI placement is critical for the accurate generation of the curves, the ROI must be placed over the parenchyma without inclusion of major bile ducts or the heart. Analysis is invalid if movement occurs. The injection technique was also found to

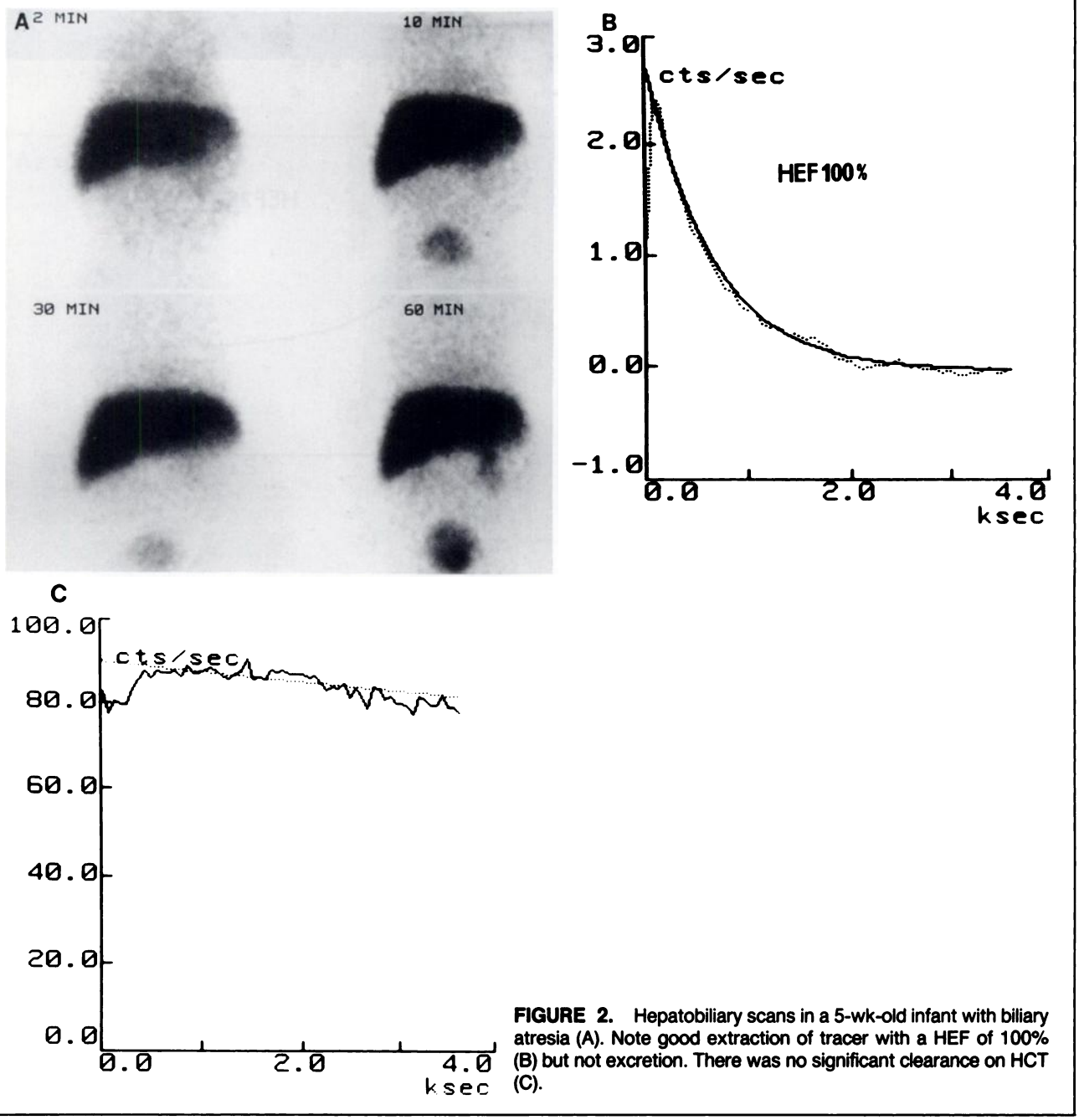

FIGURE 2. Hepatobiliary scans in a 5-wk-old infant with biliary atresia (A). Note good extraction of tracer with a HEF of 100% (B) but not excretion. There was no significant clearance on HCT (C).

be important. Because the deconvolution analysis technique requires a fast intact bolus, injections in the feet were found not to be satisfactory. Upper limb injections, preferably in the antecubital fossa, were found to be the most accurate, and a single bolus injection without flushing of the syringe was imperative.

DISCUSSION

Measurement of hepatic uptake of ^{99m}Tc-IDA compounds is considered a useful indicator of hepatocellular function (*1,4,5,9*). Hepatic uptake can be assessed by visual inspection of the scans, but visual inspection may not separate hepatocyte from the hepatic blood-pool component. What may appear as liver uptake may be due to hepatic blood pool with little hepatocyte uptake. The uptake may be quantitated, as in the current study, by measuring HEF using deconvolution analysis (*4–6*). Visual estimation of uptake by assessing blood-pool clearance is limited because it is subjective and provides no quantitation. On the other hand, assessment of HEF provides an index for quantitation which is useful in comparing different disease states or assessing the prognosis of disease in an individual patient with sequential studies (*9,10*). HEF

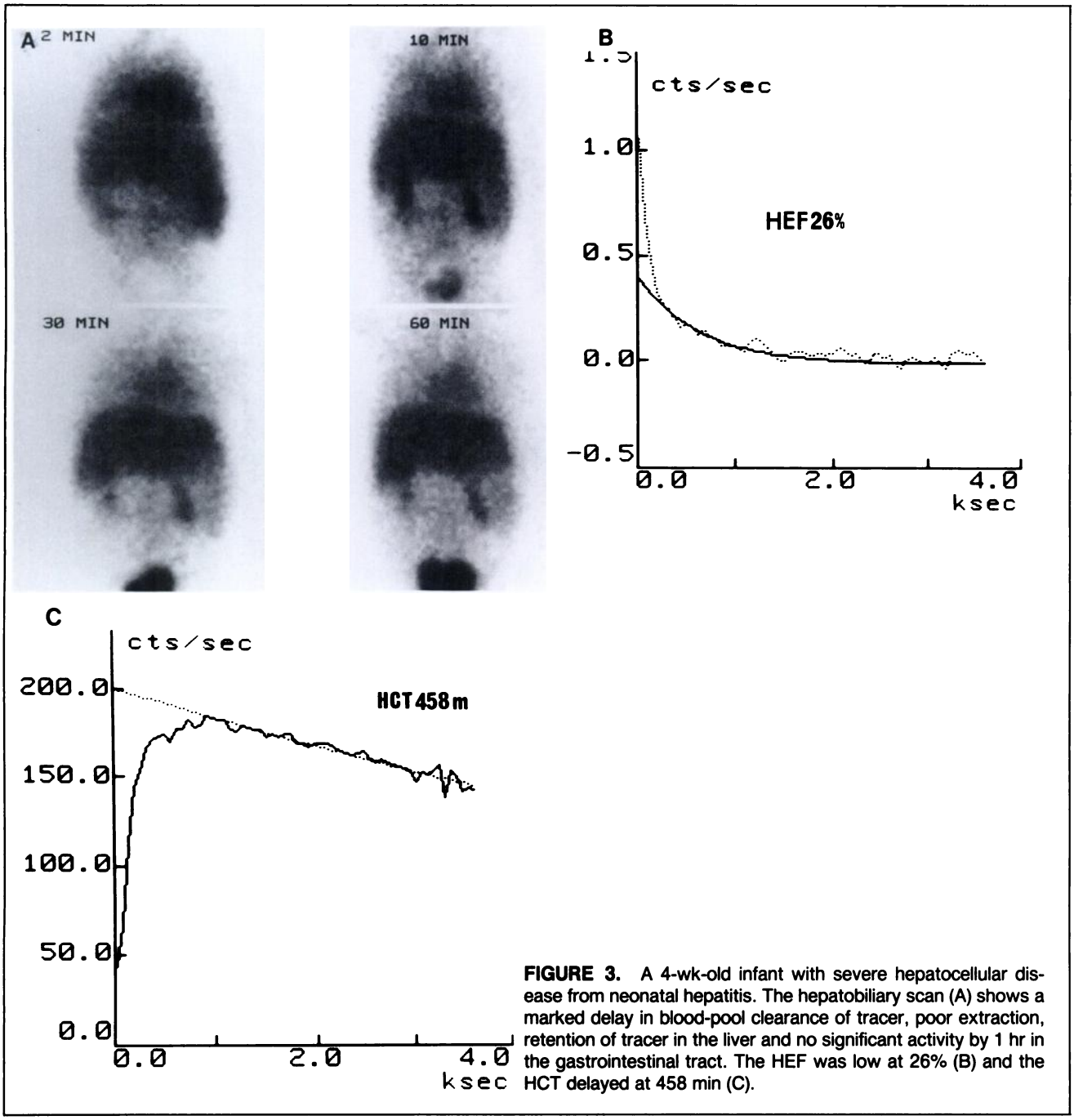

FIGURE 3. A 4-wk-old infant with severe hepatocellular disease from neonatal hepatitis. The hepatobiliary scan (A) shows a marked delay in blood-pool clearance of tracer, poor extraction, retention of tracer in the liver and no significant activity by 1 hr in the gastrointestinal tract. The HEF was low at 26% (B) and the HCT delayed at 458 min (C).

has been shown to accurately reflect hepatocyte function in adults (*4,5,9,10*).

All three groups with liver disease showed impairment of HEF, presumably reflecting liver dysfunction at the time of the test. These results were of considerable interest, since the test could seemingly distinguish the varying severity of liver and biliary tract disease. This was first evident by the significant but mild impairment of HEF in the miscellaneous group with mild liver or biliary disease in comparison to the control group. Furthermore, in those patients with more severe disease, e.g., the hepatocellular group, HEF was even more impaired in comparison with the other groups. Of note, only 1 of 9 (11%) patients with biliary obstruction had a HEF below 50% in contrast to the hepatocellular group where the HEF was below 50% in 6 of 16 (38%) patients. These differences and the range of values in both the obstructive and hepatocellular groups extending down to below 20% suggest that this may well be a sensitive test of liver function in children. Currently, liver dysfunction in children, except for biochemical tests, is difficult to assess. Although biochemical tests can assess liver dysfunction, they only provide a semiquantitative estimate and are an indirect measurement of injured liver cells, whereas HEF is a direct measurement of intact

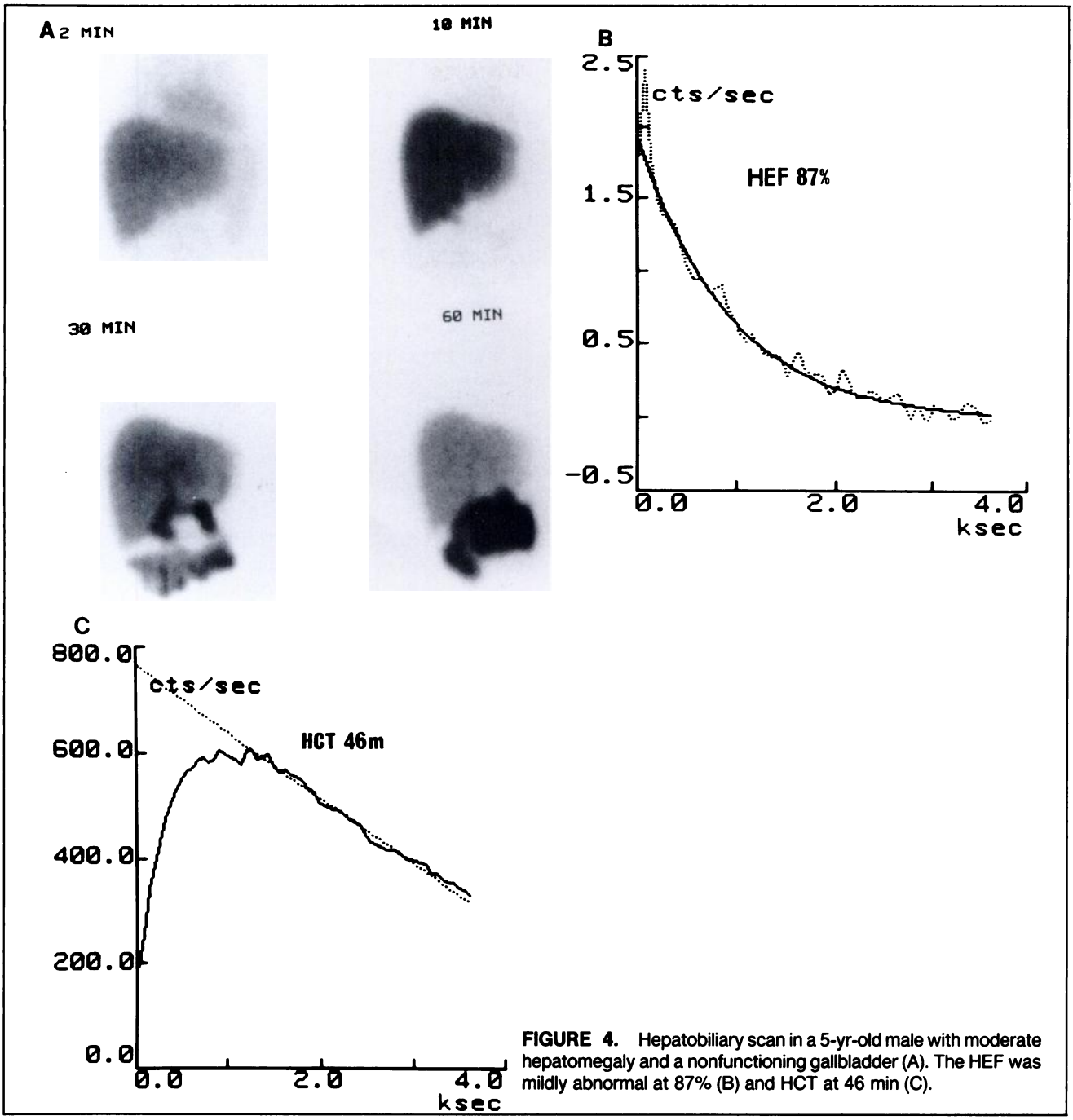

FIGURE 4. Hepatobiliary scan in a 5-yr-old male with moderate hepatomegaly and a nonfunctioning gallbladder (A). The HEF was mildly abnormal at 87% (B) and HCT at 46 min (C).

hepatocytes or hepatic reserve. Biochemical tests do not provide a quantitation of the amount of functioning residual liver tissue except in the situation where synthetic failure occurs and serum albumin and coagulation factor synthesis becomes impaired. Although we have yet to assess a wide variety of liver disease (particularly chronic liver failure) HEF may potentially be helpful in providing a quantitation of liver dysfunction or of functioning residual tissue for prognostic purposes. This would be particularly valuable to more accurately assessing patients for liver transplantation prior to the onset of severe liver failure.

The current study of deconvolution analysis and HEF in children with liver and biliary tract disease has shown similar results to those in adult populations. The study highlights, however, that deconvolution analysis cannot adequately distinguish between categories of liver disease because of overlap with normal controls. This is not an unexpected finding. One would anticipate that some patients with early obstructive biliary disease would have normally functioning hepatocytes and should have a normal HEF. In contrast, patients with obstructive disease with associated hepatocellular dysfunction would have reduced HEF (e.g., biliary atresia with associated cirrhosis of the liver). Heyman and Chapman (*11*) utilized a decon-

TABLE 1
Hepatic Extraction Fraction and Excretion $T_{1/2}$ Values in Normal Subjects and Patients with Hepatobiliary Disease

	Normal	Obstruction	Hepato-cellular	Miscel-laneous
No.	12	9	16	8
HEF%	99.0 (3.6)	79.3 (25.5)*	51.5 (20.6)†¶	87.8 (13.3)*††
HCT (min)	23.6 (7.7)	183.1 (201.1)*	101.9 (77.0)‡**	44.8 (35.7)§**

* Significant different from normal $p < 0.02$.
† $p < 0.001$.
‡ $p < 0.01$.
§ ns.
¶ Obstruction versus HCD $p < 0.01$.
** ns.
†† HCD versus miscellaneous $p < 0.001$.

volution analysis technique to determine an extraction ratio in neonates with hyperbilirubinemia and found it to be useful to distinguish biliary atresia from neonatal hepatitis syndrome in infants less than 2 mo old. Over this age, however, liver function was usually compromised in patients with biliary atresia and the extraction ratio could not differentiate biliary atresia from severe hepatocellular disease.

The excretion HCT results in the current study appear similar to the HEF results. All groups with liver disease had prolonged clearances in comparison to normal controls, although not significantly so. As expected, those with biliary tract obstruction had the most prolonged clearances, but statistical analysis did not discriminate them from either hepatocellular disease or milder liver disease. The excretion HCT does, however, measure the clearance of ^{99m}Tc-IDA from both hepatocyte and bile flow through the ducts. Thus, those patients with severe hepatocellular disease and those with obstructive disease who are likely to have a component of hepatocellular dysfunction should have prolonged clearances. In contrast to the HEF, HCT does not discriminate as well in terms of defining the severity of disease, as seen by the overlap of both the mild and more severe liver disease results compared with the controls. However, the numbers in the categories are small and a more precise estimate of HCT as a single or sequential measure of liver dysfunction, cholestasis or obstruction will only be determined with a greater number of patients with a wider variety of liver disease.

A problem with the deconvolution process found in adults and also in this group of pediatric patients was that artifacts caused by an abrupt truncation of data at the end of acquisition may occur. Juni (*5,6*) described an appended curve technique to eliminate these artifacts. A low frequency, smoothly tapering tail is added to both the bloodpool and liver curves, extending them to many times their original length. The curves fall to zero, thus eliminating the abrupt cutoff and artifacts. The two major technical problems with regards to children were patient movement and injection technique. Since the ROIs are critically placed around the cardiac blood pool and another around the liver so as not to include the right kidney, large bile ducts or cardiac structures, any movement will affect the analysis and make it invalid. A number of pediatric patients had to be excluded from this study due to this problem. It was also found that a fast intact bolus was needed to obtain accurate curves. Injections in the feet or fragmented boluses were not adequate. A single bolus injection without flushing of the syringe was necessary. The HCT technique is also applicable to pediatric patients,

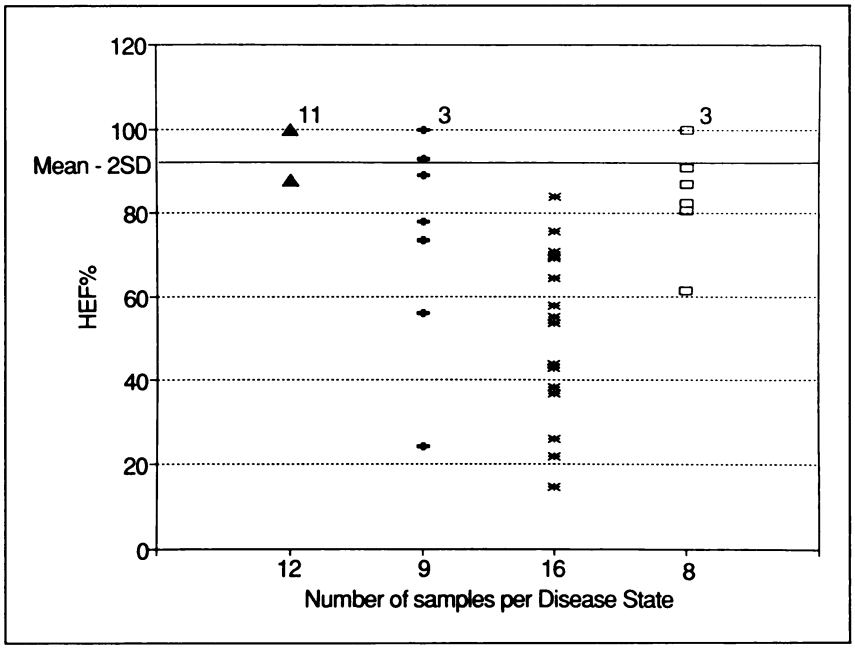

FIGURE 5. Ranges of HEF and categories of normal and hepatobiliary diseases. ▲ = normal; + = obstruction; * = hepatocellular disease; □ = miscellaneous.

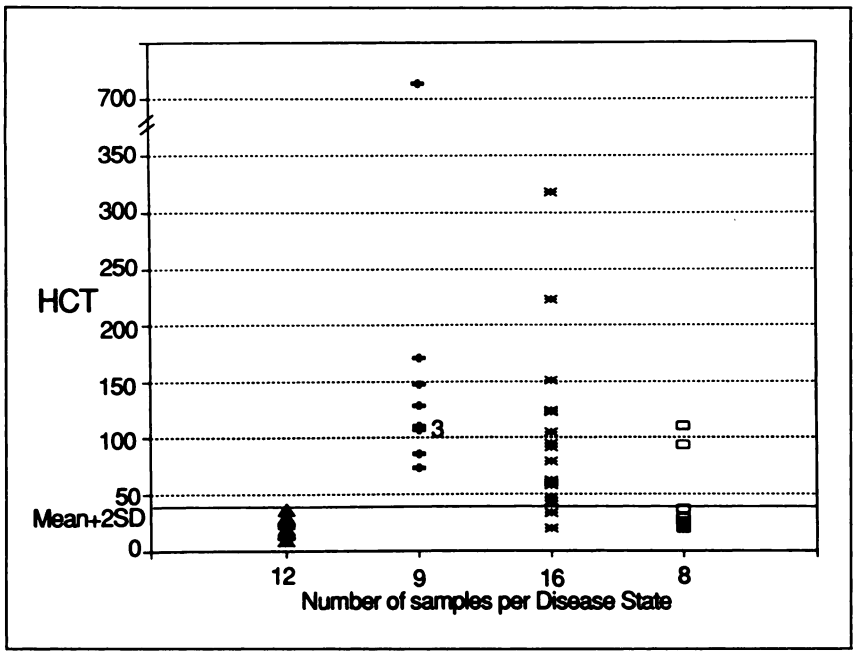

FIGURE 6. Ranges of hepatic excretion $T_{1/2}$ values and categories of normal and hepatobiliary diseases. ▲ = normal; + = obstruction ; * = hepatocellular disease; □ = miscellaneous.

however, generating a reliable clearance curve depended upon no patient movement.

CONCLUSION

This study indicates that HEF and HCT are applicable in pediatric patients as a quantitative assessment of liver function and that these methods should be incorporated into the protocols of hepatobiliary scanning. As in any quantitative measurement, the result must not be interpreted alone but in the overall context of the images, biochemical results and clinical presentation. HCT was not as valuable as HEF with regards to degree of hepatocellular dysfunction, but it can be easily generated from the same data and may add quantitative clearance data, which is most valuable in the sequential analysis of hepatobiliary studies.

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