

Reproducibility of Technetium-99m Mebrofenin Hepatic Functional Parameters Obtained with Semi-Automatic Software

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*The reliability of quantitative measurement of two hepatobiliary functional parameters using semi-automatic computer software was tested for reproducibility within and between institutions in an academic and a community hospital. Hepatic extraction fraction (HEF) and excretion half-time ($t_{1/2}$) values in ten normal controls and eleven patients were determined independently by two technologists from the same institution and one technologist from a different institution. HEF and excretion $t_{1/2}$ values were obtained using semi-automatic nuclear hepatology software and were then compared using the paired *t*-test to determine their reproducibility. There was no difference in the HEF or excretion $t_{1/2}$ values obtained independently by the three technologists. We conclude that results obtained using semi-automatic computer software for quantitative nuclear hepatology with technetium-99m IDA agents are highly reproducible and should be used routinely as a supplement to hepatobiliary imaging studies.*

The recent trend in nuclear medicine has been to incorporate quantitative measurement of function as an integral part of imaging organ morphology (1,2). This trend, already well established in nuclear cardiology, is now spreading to other organs including the liver, brain, and kidneys. In the case of the liver, two functional parameters, measured as an integral part of hepatobiliary imaging with technetium-99m (^{99m}Tc) IDA agents, not only provide a quantitative measure of organ function but also aid in differentiating biliary from hepatocyte disease (3-6).

The two parameters are hepatic extraction fraction (HEF) and hepatic excretion half-time ($t_{1/2}$). HEF is calculated by deconvolutional analysis of the first 30 min of data and is a measure of how efficiently the hepatocyte extracts the ^{99m}Tc IDA agent from the hepatic blood pool (3,7). Excretion $t_{1/2}$ is calculated by the nonlinear least squares technique using all 60 min of the data and measures how well the ^{99m}Tc IDA is secreted by the hepatocyte and how rapidly it is removed

from the canaliculi (3). It is a measure of the integrity of the hepatocyte secretory function and patency of the biliary ducts.

We have developed semi-automatic computer software in collaboration with a commercial company (ADAC Laboratories, Milpitas, CA) and applied it in preliminary clinical studies (8). This current project was undertaken to test the reproducibility of the semi-automatic software results among technologists within a department and between technologists from two different hospitals: the academic hospital's nuclear medicine department has a technologist training program, while the community based hospital's nuclear medicine department is primarily involved in patient care.

MATERIALS AND METHODS

The control subjects (Group 1) included ten normal volunteers: six males with an age range of 25-53 yr and four females with an age range of 24-43 yr. Informed consent was obtained from each volunteer. Abdominal ultrasound and liver function tests were normal. The patients (Group 2) consisted of ten males with an age range of 37-65 yr and one 37-yr-old female. The patients' total bilirubin level ranged from 0.8 to 13.3 mg% with a mean of 3.5 mg%.

After an overnight fast, each subject was positioned supine with the heart, liver, and duodenum within the field of view of a large scintillation camera fitted with a low energy, high resolution collimator. The energy spectrometer was set for the 140 keV photopeak of ^{99m}Tc using a 20% window. A 3 mCi dose of ^{99m}Tc mebrofenin (Choletec, Squibb Diagnostics, New Brunswick, NJ) was administered to each normal subject intravenously, and digital data were acquired on a computer (ADAC Laboratories, Milpitas, CA) using a $64 \times 64 \times 16$ matrix at a rate of 1 frame/min for 60 min. The dosage of ^{99m}Tc mebrofenin was based on the weight and bilirubin level of each patient and ranged from 3 to 8 mCi. The raw data disc from the VA Medical Center was taken to the community hospital where the technologist independently obtained the values by drawing the regions of interest (ROIs).

ROIs of approximately 50-70 pixels were manually drawn by each technologist over the heart, upper right lobe of the

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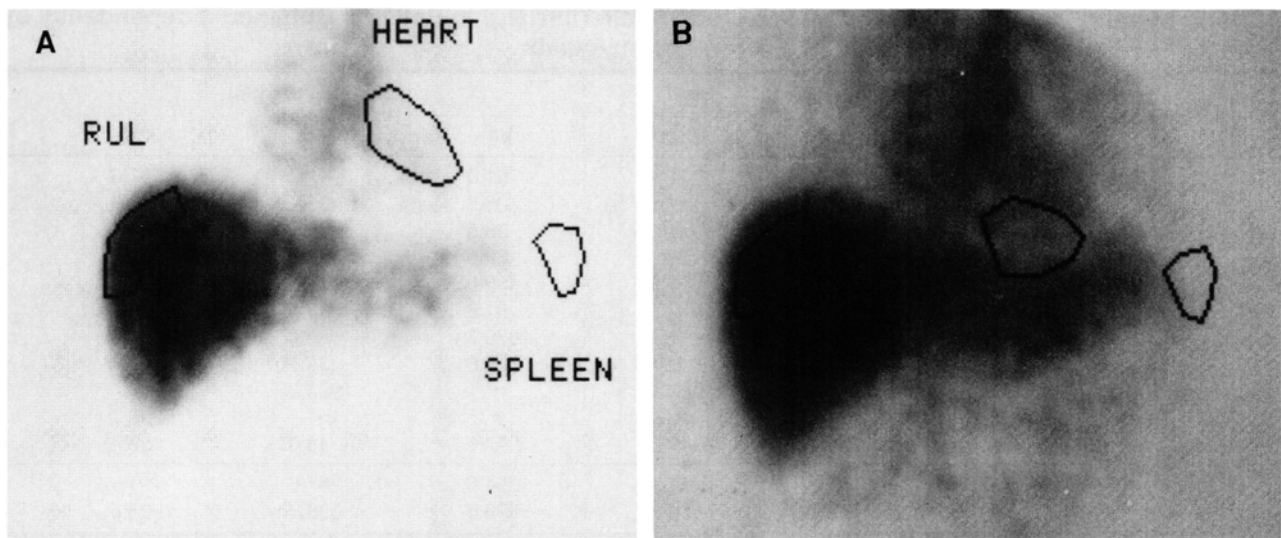


FIG. 1. Technetium-99m mebrofenin hepatobiliary images with (A) three ROIs correctly drawn and (B) the heart ROI drawn too low so that it includes part of the liver. The incorrectly drawn heart ROI caused the hepatic extraction fraction to be reduced from the actual value of 100% to an understated value of 38%.

liver, and the spleen (Fig. 1). Two technologists from the VA Medical Center (V1 and V2) and one technologist from the community hospital (C1) obtained the results. The computer presents the data in a tabular format along with the normal range.

RESULTS

The HEF and excretion $t_{1/2}$ values obtained in the control subjects are shown in Table 1. These values were compared with one another using the paired t-test. The differences between the values were statistically not significant. In all of the control subjects, the HEF was 100%. The excretion $t_{1/2}$ value for the control subjects ranged from 9.0 to 34.2 min with a mean of 14.7 min. The mean serum total bilirubin level of the patients was 3.5 mg% and the HEF values ranged

from 23–100% with a mean of 60.2% (Table 2). The excretion $t_{1/2}$ values for the patients ranged from 21.2 min to infinity.

In Table 2, the mean and s.d. of the excretion $t_{1/2}$ values obtained by technologist C1 are high because the excretion $t_{1/2}$ value of Patient 10 (6,391 min) was included in the average. The other two technologists, V1 and V2, labeled this patient value as infinity and hence did not include it in their calculation of the mean. If the excretion $t_{1/2}$ values for Patients 7, 9, and 10 are excluded, the adjusted mean and s.d. obtained by each technologist are as follows: V1:51.7,24.9; V2:55.4, 33.5; and C1:50.8, 21.5. In five cases, the excretion $t_{1/2}$ curve slopes slightly upward at 60 min, and the computer calculates a negative excretion $t_{1/2}$ value. We translated this negative value as infinity and thus did not assign it any value for the table. A downsloping excretion $t_{1/2}$ curve results in a positive excretion $t_{1/2}$ value.

TABLE 1. Hepatic Extraction Fraction and Excretion Half-Time ($t_{1/2}$) in Control Subjects Obtained Independently by Three Technologists

Controls	HEF (%)			Excretion $t_{1/2}$ (min)		
	V1	V2	C1	V1	V2	C1
1	100	100	100	10.9	10.5	10.1
2	100	100	100	12.2	14.2	11.2
3	100	100	100	12.4	12.8	18.0
4	100	100	100	11.3	11.4	10.0
5	100	100	100	9.8	10.5	10.3
6	100	100	100	31.8	34.2	32.3
7	100	100	100	17.1	16.1	18.6
8	100	100	100	17.9	17.5	16.1
9	100	100	100	9.8	9.0	10.0
10	100	100	100	9.9	10.5	—
Mean	100	100	100	14.3	14.7	15.2
s.d.	0	0	0	6.8	7.4	7.4

Note: V1 and V2 are technologists from the VA hospital. C1 is a technologist from a community hospital.

TABLE 2. Hepatic Extraction Fraction and Excretion Half-Time ($t_{1/2}$) in Patients Obtained Independently by Three Technologists

Patients	HEF (%)			Excretion $t_{1/2}$ (min)		
	V1	V2	C1	V1	V2	C1
1	71.0	79.5	78.9	51.0	47.2	67.0
2	86.5	81.6	54.8	36.6	35.4	36.5
3	77.1	88.9	100.0	28.5	26.1	21.2
4	76.0	90.2	60.4	32.0	36.2	37.7
5	50.0	60.1	54.3	89.0	117.5	86.1
6	90.4	63.6	44.6	91.8	98.4	69.2
7	22.9	24.0	23.6	1875.7	∞	414.1
8	53.4	52.1	45.8	37.6	35.1	38.5
9	32.1	35.5	36.8	∞	1963.2	∞
10	37.1	44.8	41.3	∞	∞	6390.7
11	81.0	77.2	81.7	47.6	48.0	50.4
Mean	62.6	63.4	56.6	254.6	267.5	721.14
s.d.	22.2	22.3	22.4	608.5	636.7	1995.4

Note: V1 and V2 are technologists from the VA hospital. C1 is a technologist from a community hospital.

DISCUSSION

Our results demonstrate that the semi-automatic computer software is reliable and the results are reproducible both within and between institutions. Several factors may contribute to this high degree of reliability. First, the liver is a large organ which ensures an adequate number of pixels for each ROI. Usually 50–70 pixels are included in an ROI. Normally almost all of the injected dose of mebrofenin (98.5%) is concentrated in the liver and the background contribution is negligible. In patients with high bilirubin levels, the dose can be adjusted to the bilirubin level, which compensates for the low uptake in high bilirubin patients. The displacement effect of bilirubin on hepatic uptake of ^{99m}Tc IDA agents is least with mebro-

fenin, allowing adequate hepatobiliary images even in patients with high bilirubin levels (9).

The software allows selection of as many as three ROIs over the liver. In most patients one ROI over the right upper lobe will suffice. But in some patients, the hepatic pathology tends to be regional, as in the case of sclerosing cholangitis (10,11). In these patients, the software's ability to process two or three ROIs will enable calculation of regional HEF and $t_{1/2}$ values for three regions (Fig. 2).

In order to obtain reproducible results, the ROIs must be consistently drawn. It is important to draw the cardiac region carefully so that it does not include the upper part of the liver. Otherwise, the HEF will be understated as shown in Figure 1.

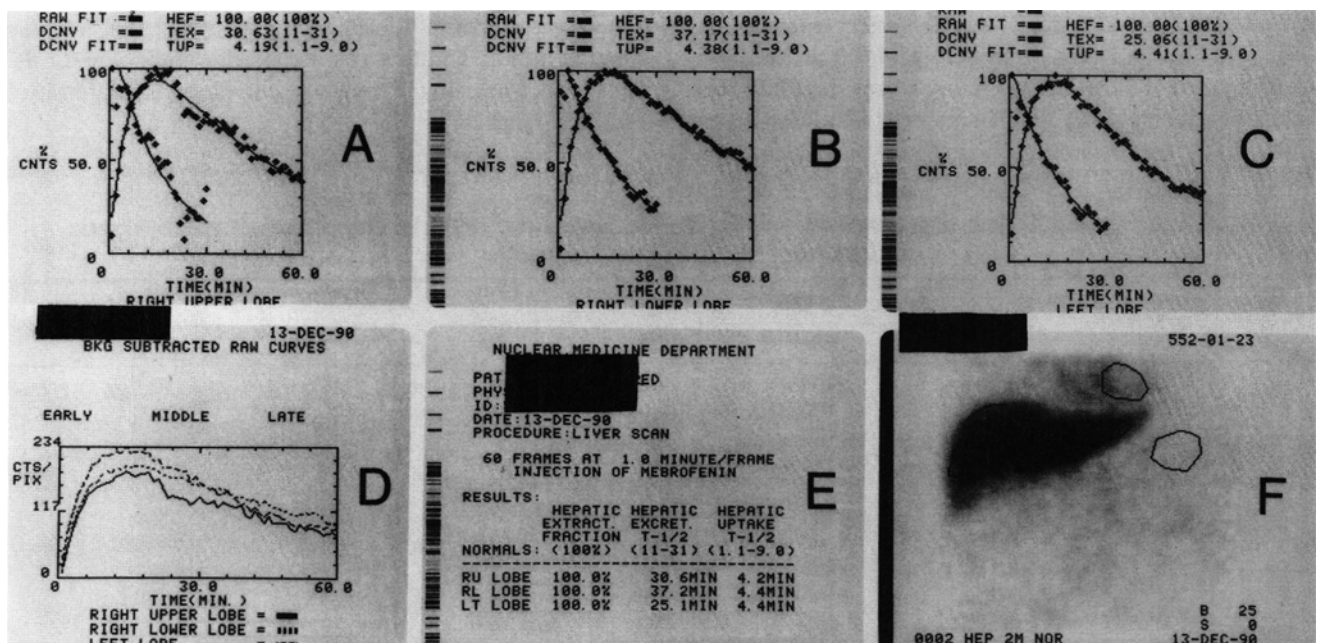


FIG. 2. Graph curves and data generated using semi-automatic computer software. The hepatic extraction fraction and $t_{1/2}$ excretion values of the (A) right upper lobe, (B) right lower lobe, and (C) left lobe of the liver are shown. The lower panel shows (D) the three excretion curves, (E) the HEF and excretion $t_{1/2}$ value for each ROI and the normal values, and (F) the ROIs drawn correctly over the images.

The inclusion of major bile ducts with the liver ROIs will affect excretion $t_{1/2}$ values. Usually it is necessary to review all 60 frames in a cine format to identify the position of the major ducts so that they can be excluded from the liver ROIs. If ROIs are not carefully drawn, the left hepatic duct and the gallbladder tend to alter the excretion $t_{1/2}$ values over the left lobe and lower right lobe, respectively.

The excretion $t_{1/2}$ value curve is usually smooth, without any zig-zag effect. If a patient coughs or moves during data collection one can easily notice this effect on the curves.

After calculating the HEF and $t_{1/2}$ values, the computer presents these values in a graphic form along with the normal values. When three ROIs are drawn, the computer presents the values for all three regions along with the graph curves (Fig. 2).

After the technologist has collected the hepatic phase data for 60 min, the time necessary for the data analysis and presentation of results ranges from 8–10 min. Since the graphic presentation is software-controlled, very little of the technologist's time is taken for data presentation. There is no need for any manual calculation.

Our physicians include the HEF and the excretion $t_{1/2}$ values in a tabular form in the patient report. These values enable the nuclear medicine physician to differentiate biliary and hepatic disease in their early stages (2,3,5,6,12–15). The HEF value remains high in biliary obstruction and low in hepatocellular disease. Such distinction between hepatocellular disease and biliary disease is difficult to make from the images alone (2). In advanced biliary disease, the HEF tends to be low due to the effect of biliary obstruction on the hepatocytes. Now, with the ability to measure these physiologic parameters, the quantitative difference between hepatocellular disease and biliary obstruction is readily accomplished. These same parameters can also be used to test the benefits of therapy. If the therapy is successful, the HEF and excretion $t_{1/2}$ values will improve (2).

CONCLUSION

It is evident from our results that quantitative nuclear hepatology is attainable in both a large academic institution and in a small community hospital. The measurement of such parameters is included as part of the education in our technologist training program and the students are able to apply this technology immediately after graduation. We hope that with the availability of the validated software, nuclear medicine physicians will provide quantitative nuclear hepatology

parameters routinely, as has been done with nuclear cardiology parameters for well over ten years. The time has come for quantitative nuclear hepatology to be treated as a mature technology and for it to be applied widely and routinely in clinical nuclear medicine practice.

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