Xenon-133 Hepatic Retention Ratio: A Useful Index for Fatty Liver Quantification

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Xenon-133 hepatic retention ratio was developed for quantifying fatty liver. Data were acquired in frame mode in the hepatic region and both lung bases for 5 min after rebreathing 20 mCi of gaseous ^{133}Xe and for another 5 min during washout. Static [^{99m}Tc]sulfur colloid liver imaging was performed with the patient in the identical position immediately after the ventilation study and data were stored for liver localization. A hepatic time-activity curve corrected for background activity was generated. The ^{133}Xe retention ratio was derived by dividing the activity at 3.5 min after washout by the peak activity. The data of 16 controls and 20 patients with fatty liver were analyzed. The retention ratio (mean ± s.d.) was greatly increased in patients with fatty infiltration (0.43 ± 0.20 vs. 0.04 ± 0.08 in controls, $p < 0.001$). There was a strong positive correlation between the ^{133}Xe retention ratios and percentage of fat on biopsy as assessed by the amount of the liver tissue occupied by fat globules on H & E stained sections. The ^{133}Xe hepatic retention ratio is a simple, accurate and clinically useful index of detecting, quantifying and managing fatty infiltration of the liver.

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Fatty infiltration of the liver, a commonly encountered disorder, has been associated with alcohol abuse, obesity, diabetes mellitus, exogenous steroids, presumed malnutrition accompanying chronic wasting conditions, i.v. hyperalimentation, Reye's syndrome, severe hepatitis, jejunoileal and jejunocolic bypass for obesity, glycogen storage disease, cystic fibrosis or blunt hepatic trauma (*1*). Although this disorder per se is a relatively harmless process (*2*), its continuation may lead to rather severe sequelae including cirrhosis (*3,4*). Clinically, the patient usually does not have specific gastrointestinal symptoms (*5*) but often has hepatomegaly (*6*). There is no apparent correlation between the magnitude of biochemical abnormalities and the degree of fatty infiltration in most cases (*5,7*). Accordingly, quantification of fat content of the liver is required not only for detection but for management of fatty liver.

Computed tomography (CT) number in EMI units has been used for estimating fat content of the liver (*8*). This technique is brief, requiring only a single 20-sec scan and no oral contrast medium or muscle relaxant. However, CT numbers are subject to errors caused by changes in the frequency of x-rays as they transverse the patient and changes in other factors (*8*).

Nuclear magnetic resonance imaging studies using conventional spin-echo techniques are insensitive in the detection of fatty liver (*9–11*). Recently, lipid signal fraction or percent lipid signal has been derived from the proton spectroscopic imaging technique and used for quantifying fatty infiltration of the liver (*12*). In addition to its high sensitivity, this technique carries the advantage of improving tissue specificity by the ability to differentiate changes in the T2 of hepatic water and hepatic lipid. The lipid signal fraction reflects the number of fatty acid protons imaged and not the weight per volume of lipid. This technique may cause a slight underestimation of the amount of hepatic fat present because of partial misregistration of protons attached to the fatty acid molecule. This inaccuracy may arise since the protons in the CH_3 group at the end of each fatty molecule have precessional properties different from those of both water molecules and the CH_2 groups of the fatty acid molecule (*12*). In addition, interference from other proton-containing compounds in the liver, such as glycogen and lactate, has not been taken into account (*12*).

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Xenon-133 (^{133}Xe) almost instantaneously exchanges with the tissue space at the capillary level (*13,14*) and the organ ^{133}Xe activity is proportional to the blood flow and differential tissue solubility, namely, partition coefficient (*13,15,16*). There is a high solubility of ^{133}Xe in fat (*13,15,17*). Accordingly, ^{133}Xe has a greater concentration associated with a slower washout in fatty liver after 3 to 5 min of rebreathing the gas despite a low blood flow to fat (*13,16*). This has led us to develop an index, ^{133}Xe hepatic retention ratio (HRR), useful for quantitating fatty liver (FL). A portion of this work has been published earlier in abstract form (*18*).

METHODS

A digital gamma camera (Elscint Apex 410) was linked to a minicomputer (Sopha Medical System 5000), and the data stored on computer disks. Data were acquired in frame mode at 0.5 min per frame in the hepatic region and both lung bases in A-P view with the patient in the supine position for approximately 5 min after rebreathing 20 mCi of gaseous ^{133}Xe (in 100% of oxygen) in a closed-circuit rebreathing system (Radx Ventil-Con II-143) and approximately for another 5 min after washout. A liver image was then performed as usual with the patient and the camera in the identical position after i.v. injection of 5 mCi of technetium-99m (^{99m}Tc) sulfur colloid. Data were also acquired simultaneously in frame mode of 64 × 64 matrix for 1 min. A computer routine was then used to calculate the hepatic retention ratio. To obtain this ratio, a series of operation was carried out as shown in Figure 1. Three regions of interest (ROIs) corresponding to the lower half of the right hepatic lobe, lung, and spleen were set in the colloid image. The splenic ROI was used for background correction, and the splenic activity was normalized for the area of the hepatic ROI. The ROIs in the same areas were also set by a double cursor technique in the ^{133}Xe study. The time-activity curves (TACs) for the lung, liver, and spleen were generated. The hepatic TAC corrected for background was obtained, and time to start washout was observed from the pulmonary TAC shown in the green vertical line. The hepatic retention ratio was then derived as follows:

$$\text{HRR} = \frac{A}{B},$$

where B and A were equal to the peak hepatic activity and that at 3.5 min after washout, respectively. In all cases studied, visual assessment of local hepatic ^{133}Xe uptake was performed to exclude any case with focal fatty infiltration of the liver (*19*), since our study was confined to the diffuse type of fatty infiltration.

The intraobserver variation for determining HRR was assessed by having an operator repeat each analysis 1–5 days later without knowledge of the previously determined results. All ratio determinations were performed by experienced operators who were unaware of the clinical diagnosis. To determine the interobserver variation of the technique, the ratios obtained in study 1 and study 2, study 1 and study 3, and study 2 and study 3 were determined for each patient. Linear regression equations and correlations were obtained in a standard manner.

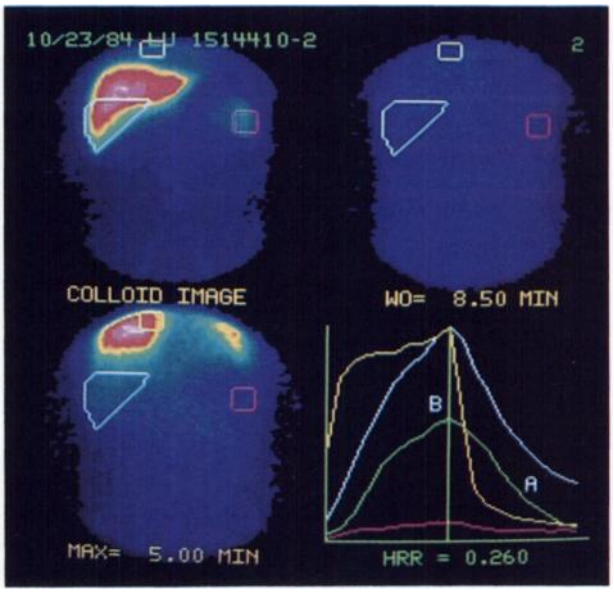

FIGURE 1
Color TV display showing derivation of hepatic retention ratio. Setting of hepatic, pulmonary, and splenic ROIs is shown in colloid image (upper left), at peak after washout (lower left), and at 3.5 min after washout (upper right). Splenic ROI is used for background correction, and the splenic activity is normalized for the area of the hepatic ROI. Pulmonary time-activity curve (TAC) is shown in yellow, gross liver TAC in white, background activity in red, and hepatic TAC corrected for background in green. Time to start washout is observed from pulmonary TAC shown in green vertical line. Let B equal peak hepatic activity and A equal that at 3.5 min after washout. HRR is then defined as A over B.

Regression plots for determining the intra- and interobserver errors for HRR are illustrated in Figures 2 and 3. The degree of intra- and interobserver agreement was very high, reflecting the ease with which the reproducible results can be obtained.

Liver biopsies were obtained within 24 hr of the xenon studies. Histologic specimens were assessed—without the knowledge of HRR—on the basis of the amount of the liver tissue occupied by fatty vesicles on H & E stained sections. The result was expressed in the relative area of fat vacuoles as a percentage of the section. In detail, fat globules in each biopsy specimen were counted by using the Olympus micrometer 10/10 SQ with a 400× magnification. There was a square in the eyepiece, consisting of one hundred small checks. Under each high power field, the number of checks in the square occupied by the fat globules were counted, the whole specimen was examined square by square in due order, and then the percentage of the section occupied by the fat was calculated.

The intra- and interobserver variations for determining the percentage of fat on biopsy were assessed in a similar way to determining the variations in obtaining HRR. They were both small ($r = 0.97$, s.e.e. = 2.79, $y = 0.86x - 0.66$, $p < 0.001$, $n = 11$ for intraobserver variability; $r = 0.94$, s.e.e. = 4.13, $y = 0.82x + 0.72$, $p < 0.001$, $n = 11$ for interobserver variability).

From June 1984 to April 1985, ^{133}Xe retention ratios were determined in 41 patients with strong indications of fatty liver.

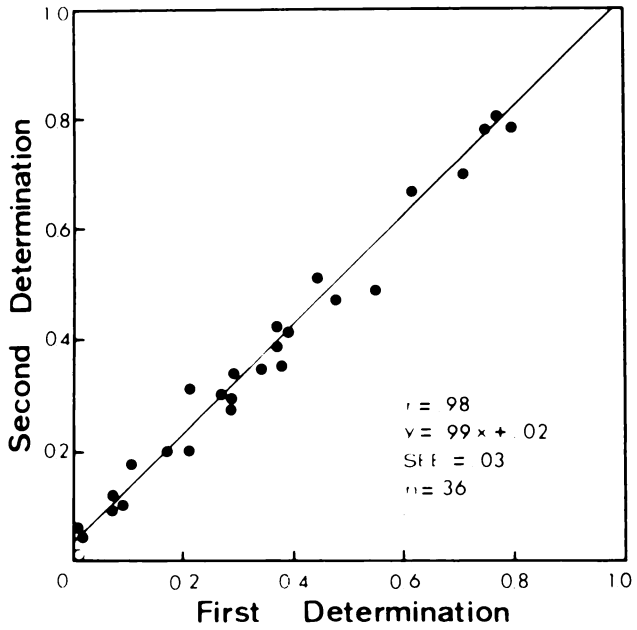

FIGURE 2
Plot of first compared with second determination of ^{133}Xe hepatic retention ratio. Note very high intraobserver agreement.

In 20 cases (18 male, 2 female) with a mean age of 50.8 yr (range 29–70) yr, proof of fatty liver was obtained by liver biopsy. Fifteen of twenty patients had alcoholic liver disease and five had chronic hepatitis. These cases form the basis of this report. HRR was also determined in a control group consisting of ten volunteers without evidence of hepatobiliary disease and six patients with chronic hepatitis but without fatty change demonstrable by liver biopsy. Their mean age was 29.7 yr with a range of 22 to 64 yr.

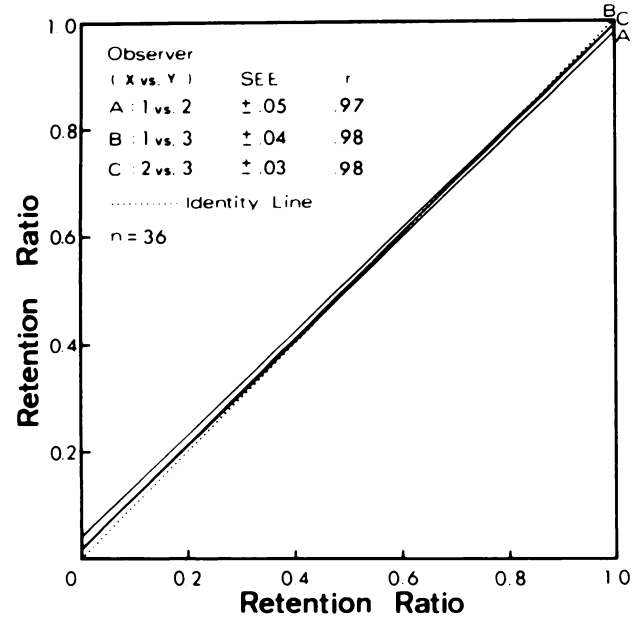

FIGURE 3
Regression equations obtained for ^{133}Xe hepatic retention ratio from paired observers (1,2,3) in same 36 subjects. Note excellent correlations.

In order to know what conditions might cause false positive evaluation of the ratio, the ratio determinations were done in five additional proven patients with chronic obstructive pulmonary disease (COPD) and eight individuals with normal liver function tests (bilirubin, serum protein, SGOT, SGPT, alkaline phosphatase) in the basal condition and in postprandial hepatic hyperemia (*20*). In the later case, the ^{133}Xe retention ratios were determined after an overnight fast at Day 1 and 20 min after oral administration of 300 ml of liquid meal (300 kcal, VITAL High Nitrogen, Ross Laboratories, Columbus, OH) at Day 2.

Student's t-test for unpaired data (two-tailed) was used to test the significant difference in mean between the control and patients. A probability (p) value < 0.05 was considered significant.

RESULTS

The mean retention ratio ± 1 s.d. was greatly increased in patients with FL (0.43 ± 0.20 vs. 0.04 ± 0.08 in controls, $p < 0.001$). The sensitivity and specificity for diagnosing FL at the optimal threshold of 0.21 was 95% and 94%, respectively. The good separation between controls and patients is clearly shown in Figure 4. There was a strong positive correlation between the retention ratios and percentage of fat on biopsy in these 20 patients (Fig. 5, $r = 0.93$, s.e.e. = 0.07, $p < 0.01$). A large area of focal hepatic ^{133}Xe uptake in the right lobe with a retention ratio of 0.31 was noted in one of 41 cases of our study. Focal fatty infiltration was confirmed by liver biopsy.

The individual ^{133}Xe retention ratios in five patients with COPD were 0, 0, 0, 0, and 0.12, falling within the normal limits. All eight normal individuals had zero retention ratios in the basal condition and after the meal.

DISCUSSION

Sutherland et al. (*21*) showed that the uptake of ^{133}Xe by the liver correlated well with the presence of fat in the liver as seen on needle biopsy, and suggested the possibility of quantitation of this observation. Ahmad et al. (*22*) reported on a quantitative correlation in rats with ethanol-induced fatty liver, and on histologic grading and the visual grading of xenon uptake in 45 patients. After his initial observation (*21*), Sutherland together with Palser (*23*) developed a calculated ratio of liver: lung xenon activity at the end of the washin phase for quantitating fatty liver. Although such an approach is able to obtain a calculated ratio at the end of the washin phase rather than a visual impression at the end of washout, the establishment of equilibrium conditions is a prerequisite to the use of this test in a

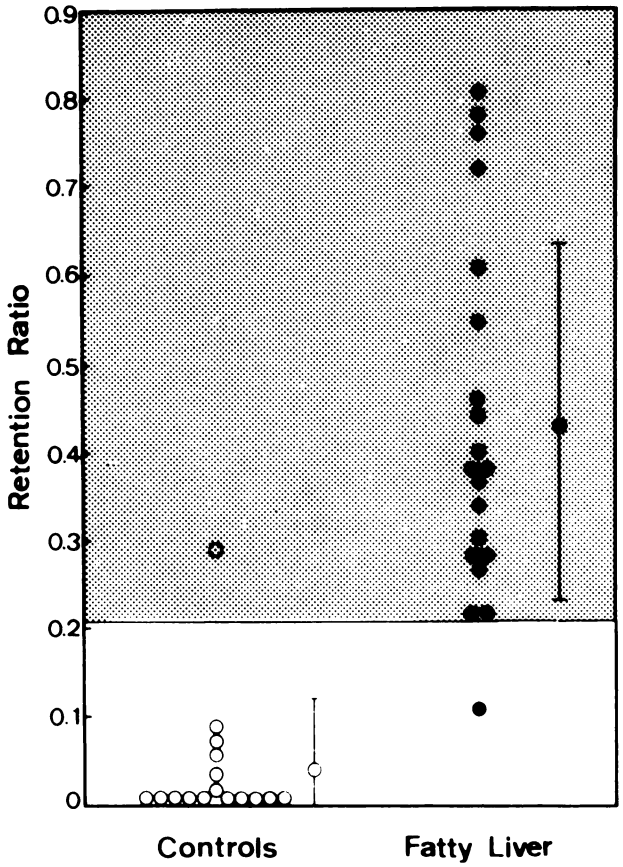

FIGURE 4
Xenon-133 hepatic retention ratio in 20 patients with fatty liver and 16 control subjects. Note good separation of controls from fatty liver. Mean values with standard deviations for control subjects and patients are indicated to side of values of each corresponding group.

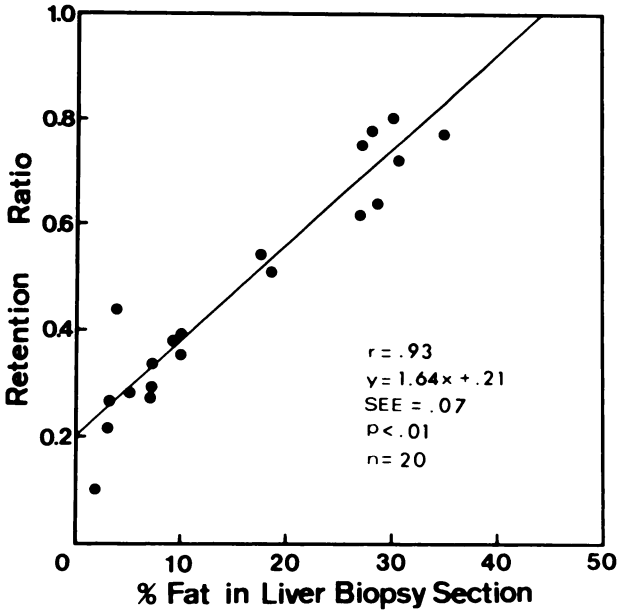

FIGURE 5
Comparison of hepatic retention ratio with percentage of fat in histologic section of liver biopsy in 20 subjects.

quantitative fashion (*23*). If the activity in the liver does not reach a plateau at the end of washin phase in the case of extensive fatty infiltration, the ratio of liver : lung xenon activity will underestimate fat content with a misleading result (*23*).

On the other hand, the ^{133}Xe hepatic retention ratio is determined by the hepatic activity at 3.5 min after washout over the peak hepatic activity. This approach has permitted us to get away from the problem of not reaching equilibrium conditions after starting washout, thereby obviating the difficulty in obtaining correct results in severe fatty infiltration by the calculated ratio of the liver : lung xenon activity.

The results in the current study indicate that the ^{133}Xe hepatic retention ratio is an objective and useful parameter for detecting and quantification of fatty infiltration of the liver. The retention ratio was greatly increased in the patients with FL as compared to normal individuals ($p < 0.001$), having the sensitivity and specificity for diagnosing FL of 95% and 94%, respectively. There was a strong positive correlation between HRR and fatty change as observed histologically.

In this study all five patients with COPD had HRR within normal limits. This indicates that COPD, where there is prolonged washout over the lungs, does not increase hepatic retention ratio. Postprandial mesenteric hyperemia has no effect on ^{133}Xe retention ratio either. Both COPD and increase in hepatic blood flow will not cause false-positive elevation of the ratio.

Focal fatty infiltration is a relatively rare entity on the one hand, and predominantly subcapsular in location on the other (*24*). In view of its subcapsular location, the lesion may overlap the basal portion of the right lung or the fatty mesentery, and it would be hard to define an exact ROI of the lesion. Accordingly, the current report has been geared to the diffuse type of fatty infiltration only. However, HRR may be determined so long as the localized fatty infiltration is large enough to show up the localized accumulation of ^{133}Xe as illustrated by our only case of large focal fatty infiltration. The ratio was 0.31, far beyond the normal values. In this particular case, the region of interest could be defined during image processing.

Since the radioactivity in the liver and spleen is not obvious during washout, the colloid image is required to set the hepatic and splenic ROIs. Such an image was necessary in all cases. In view of the diffuse nature of FL in our study, the ROI was set over the lower half of right hepatic lobe to get away from the overlying lung activity and ^{133}Xe accumulation in the fatty mesentery. The splenic ROI is most suitable for background correction. Most likely, this is due to the approximation of ^{133}Xe scattering from the lung in this region to that in the hepatic region.

The hepatic retention ratios for the 20 patients who

were thought to have fatty liver but who did not have biopsies turned out to be abnormal, being 0.36 ± 0.19. In view of no biopsies performed, these cases have not been included for analysis in this article.

Correlation of ^{133}Xe retention ratio with CT or magnetic resonance imaging has not been performed by the authors. The correlation among the three techniques will be done in the same group of the patients at the same time when the MR imaging system is installed in our institute.

The determination of ^{133}Xe retention ratio may provide a noninvasive technique for estimating liver fat content with an accuracy comparable to the histologic technique. This method may be particularly valuable in patients with severe fatty liver in whom liver biopsy is prevented by a coagulation disorder. Follow-up HRR determinations may also be helpful in monitoring fat clearance from the liver during treatment. In addition, ^{133}Xe retention ratio has high sensitivity (95%) and specificity (94%) for diagnosing FL. Furthermore, it is easy to obtain the reproducible results. Thus, HRR is a simple, accurate, and clinically useful index of detecting, quantifying, and managing fatty infiltration of the liver.

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