Xenon-133 Accumulation in Hepatic Steatosis

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Observation of radioxenon accumulation in the liver of patients during routine pulmonary ventilation studies suggested that hepatic xenon accumulation might result from increased hepatic fat content. Hepatic xenon-133 accumulation was studied in paired rat litter mates, one with alcohol-induced fatty liver, the control fed isocaloric glucose. Xenon accumulation was increased in fatty livers and paralleled the amount of liver fat. During routine ventilation studies in 42 patients, hepatic xenon accumulation and retention were correlated with alcoholic drinking history and hepatic function studies. Of 15 patients without xenon accumulation, 1 had a drinking history. Of 13 patients with 1+ hepatic xenon, five had a drinking history, three were diabetic, two were obese, and two had elevated lipid levels. Of six patients with 2+ hepatic xenon, four had a drinking history, one had no drinking history recorded, and one was diabetic; two had abnormal liver-function studies. All five patients with 3+ hepatic xenon had a drinking history and abnormal liver function. Of three patients with 4+ hepatic xenon, two had a drinking history and abnormal liver function; the other was an obese diabetic. There was a parallel between the degree of hepatic xenon accumulation and the degree of suspected alcoholic fatty infiltration or diabetes determined from the clinical data. These results suggest the possible utility of hepatic radioxenon accumulation as a diagnostic test for fatty infiltration of the liver.

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Hepatic steatosis can be associated with a variety of diseases but is frequently encountered in patients with a history of excessive use of alcoholic beverages (*1*). Fatty infiltration of the liver may be associated with a variable symptom complex and may simulate an acute surgical abdomen or obstructive jaundice, may produce manifestations of portal hypertension or symptoms of acute hepatic failure, and may eventually lead to cirrhosis (*1,2*). Sudden unexpected death has also been attributed to fatty infiltration of the liver (*3*). Liver biopsy represents the only *certain* method of establishing the diagnosis (*4*). Carey et al. (*5*) in 52 consecutive studies found 20 cases with right upper quadrant xenon-133 activity. In eight of the cases, the activity was thought to affect the interpretation of the xenon clearance from the right lung base. Clinical data were suggestive of liver dysfunction, and it can be speculated that increased activity might have been related to fatty infiltration of the liver. Studies by Kitani and Winkler (*6*) showed that the solubility of Xe-133 in human liver tissue in vitro correlated positively with the triglyceride content. These reports—together with consideration of the physical characteristics of xenon (*7*) and with our observations, during routine pulmonary ventilation studies, of increased radioxenon accumulation in the livers of patients suspected of fatty infiltration—suggested that the increased hepatic xenon in these patients might have resulted from increased hepatic content of fat.

In order to evaluate this hypothesis, we studied

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hepatic Xe-133 accumulation in rats with alcohol-induced fatty livers and assessed the relationship of the degree of xenon accumulation to the amount of hepatic fat. The possible utility of hepatic radioxenon accumulation as a diagnostic indicator of fatty infiltration of the liver in the differential diagnosis of hepatomegaly was also assessed in 55 patients during routine pulmonary ventilation studies.

MATERIALS AND METHODS

Animal experiments. Female, Holtzman strain, Sprague–Dawley rats weighing approximately 100–150 g were maintained in groups of the two weanling litter mates in a controled environment with 12-hr day/night light cycling, and were fed a diet of Purina Rat Chow and tap water ad libitum until the period of study. Principles of Animal Laboratory Care as established by the National Institutes of Health and promulgated by the American Association of Laboratory Animal Science were followed. The induction of fatty liver was accomplished in the experimental member of the pair by administration of a single dose of ethanol: after 8 hr of fasting, the experimental member was given 7.5 g per kg ethanol in a 50% aqueous solution by stomach tube and the control member of the pair received an isocaloric amount of glucose (*8*). Sixteen hours later two animals, experimental and control, were placed in a 6-l closed chamber containing 300 μCi of Xe-133 and were allowed to breathe for 5 min to equilibrium. Both animals were then simultaneously killed by occluding the airway and delivering a blow to the head. The abdomen was opened and three samples of approximately 1 g each were taken from the liver and immediately sealed in a 3-ml syringe. Radioactivity in each sample was determined in a well scintillation counter.* Subsequently each sample, and the entire liver, were weighed. In selected instances, liver tissue was processed for histologic staining and evaluated for fat content by light microscopy.

Total lipid was then extracted from the liver samples and measured as weight of dried extract by the method of Folch (*9*). This method consists of homogenizing the tissue with a 2:1 chloroform–ethanol mixture and washing the extract by addition of 0.2 volume of water. The resulting mixture separates into two phases, the lower of which is the total pure lipid extract. The washing procedure removes essentially all of the nonlipid contaminants from this extract along with a very small amount of tissue lipids. Total lipids were determined gravimetrically after evaporation of the solvent under nitrogen and drying in a dessicator until constant weight of dried lipid was achieved. The weight of the lipid was expressed as milligrams of lipid/g liver.

Human studies. Fifty-five consecutive patients referred for a pulmonary ventilation/perfusion study were evaluated. The Xe-133 ventilation study was performed before the perfusion study. Patients were examined in the upright position with the detector fitted with a low-energy diverging collimator positioned posteriorly to include as much as possible of the liver in the field of view. Ventilation was assessed for 4 min during the inhalation (washin phase) of 5–7 mCi of Xe-133 from a closed-circuit rebreathing system.† Following the initial washin and rebreathing to equilibrium, the closed-circuit system was opened to room air and the patient began a 10-min washout phase. All counting data were digitized and stored in sequential-frame mode in a 64 $\times$ 64 matrix in a dedicated computer/camera system. Regional distribution of ventilation and xenon distribution in the liver were evaluated by visual assessment of the sequential displays. Hepatic xenon retention was graded visually from 0 to 4+. No activity discernible in the hepatic area at any time was graded 0. Visible hepatic-area activity was graded as 1+. Activity comparable to the greatest intensity in the lung, present in the liver at the end of the 10-min "washout phase," was graded as 4+. Increasing activity between 1+ and 4+ was graded 2+ or 3+.

History and physical findings, height and weight, history of alcoholic drinking within the 3 weeks prior to the study, hematocrit, hepatic function studies, and other pertinent data from the patient's chart, were evaluated and compared with the accumulation and retention of radioxenon by the liver. Liver function was considered abnormal if two or more of the following parameters were abnormal: (1) elevated serum glutamic oxaloacetic transaminase (SGOT), elevated lactic dehydrogenase (LDH) or elevated alkaline phosphatase; (2) elevated serum bilirubin; (3) decreased serum albumin with increased serum globulins; (4) prolonged prothrombin time; or (5) hepatomegaly with no cause indicated other than alcoholic intake.

RESULTS

Animal experiments. The results of the rat experiments are presented in Table 1. Each result concerns a pair of matched litter mates, one with alcohol-induced fatty liver and the other a normal control. The ratios represent the comparison of the hepatic lipid content in the experimental animal with that of the control animal, and the comparison of the hepatic xenon content in the experimental animal with that in the control. Alcohol induced a 23–206% increase in hepatic fat content by comparison with the individual control litter mate. The xenon content of the fatty liver closely paralleled the lipid

TABLE 1. COMPARISON OF HEPATIC XENON AND LIPID RATIOS IN RATS

Rat pair	Lipid content: Control liver (mg lipid/g)	Lipid content: Fatty liver (mg lipid/g)	Lipid ratio mg/g fatty liver* mg/g control liver†	Xenon-133 ratio cpm/g fatty liver cpm/g control liver	Xenon ratio Lipid ratio
1	49.8	83.2	1.65	1.47	0.89
2	54.2	112.2	2.07	1.99	0.96
3	50.4	62.0	1.23	1.41	1.15
4	47.8	98.4	2.06	1.65	0.80
5	61.0	126.8	2.08	2.07	1.00
6	50.6	68.0	1.34	1.43	1.07
7	54.0	103.2	1.91	1.72	0.90
8	53.0	140.4	2.65	2.17	0.82
9	55.6	159.2	2.86	2.57	0.90
10	54.2	165.4	3.05	2.86	0.94
11	57.2	84.2	1.47	1.49	1.01
12	55.2	69.0	1.25	1.38	1.10
13	59.4	149.6	2.52	2.57	1.02
Mean ± s.d.	54.03 ± 3.81	109.4 ± 36.0	2.01 ± 0.62	1.91 ± 0.51	0.97 ± 0.11

* Alcohol-induced fatty liver.
† Isocaloric glucose-fed control.
s.d. = standard deviation.

content (see Table 1). Comparison of liver tissue obtained from control and alcohol-treated animals revealed histologic changes consistent with fatty infiltration in the liver of the alcohol-treated rat.

Human studies. Thirteen of the 55 patients did not have the liver in the field of view during the xenon ventilation, and were excluded from the study. A comparison of the hepatic xenon accumulation and retention with alcoholic drinking history and hepatic function studies was made in the remaining 42 patients (see Table 2). Of 15 patients with no hepatic xenon accumulation, eight had abnormal liver studies but only one had a history of excessive drinking. Of 13 patients with 1+ hepatic xenon accumulation, five had a positive drinking history; three of the nondrinkers, however, were untreated diabetics, two were grossly overweight, one had elevated serum cholesterol, and one had elevated serum triglycerides. Of six patients with hepatic xenon accumulation graded as 2+, four had a positive drinking history; two of the six had abnormal liver-function studies, and one of the nondrinkers was diabetic. There were five patients with 3+ hepatic xenon, and all had abnormal liver-function studies and a positive history of drinking. Of three patients with 4+ hepatic xenon, two had a positive drinking history and abnormal liver function studies and the other was an obese diabetic.

TABLE 2. HEPATIC XENON ACCUMULATION IN 42 PATIENTS COMPARED WITH DRINKING HISTORY AND LIVER FUNCTIONS

Intensity of hepatic xenon	No. of patients	Drinking history: Positive	Drinking history: Negative	Liver function abnormalities
0	15	1	14	8
1+	13	5	8*	3
2+	6	4	2†	2
3+	5	5	0	5
4+	3	2	1‡	2

* Three of these patients were untreated diabetics. Two were grossly overweight. One patient had elevated serum cholesterol, and one had elevated serum triglycerides.
† One patient with history of drinking not recorded was considered negative. The other patient was diabetic.
‡ Patient had adult-onset diabetes and was also obese.

A representative patient study is presented in Fig. 1. There appeared to be a parallel between the degree of hepatic xenon accumulation and the degree of alcoholic fatty infiltration suspected from the clinical data. Hepatic radioxenon uptake was uniform throughout the hepatic area of all patients with accumulation. Although hepatic uptake was seen in patients who were grossly obese, such uptake was localized to the area of the liver and was not present diffusely throughout the panniculus. Xenon accumulation in the liver graded as 2+ or greater correlates well with a positive drinking history or the presence of diabetes mellitus.

DISCUSSION

Hepatomegaly is one of the most common abnormalities in diffuse hepatic disease (*10*) and in the

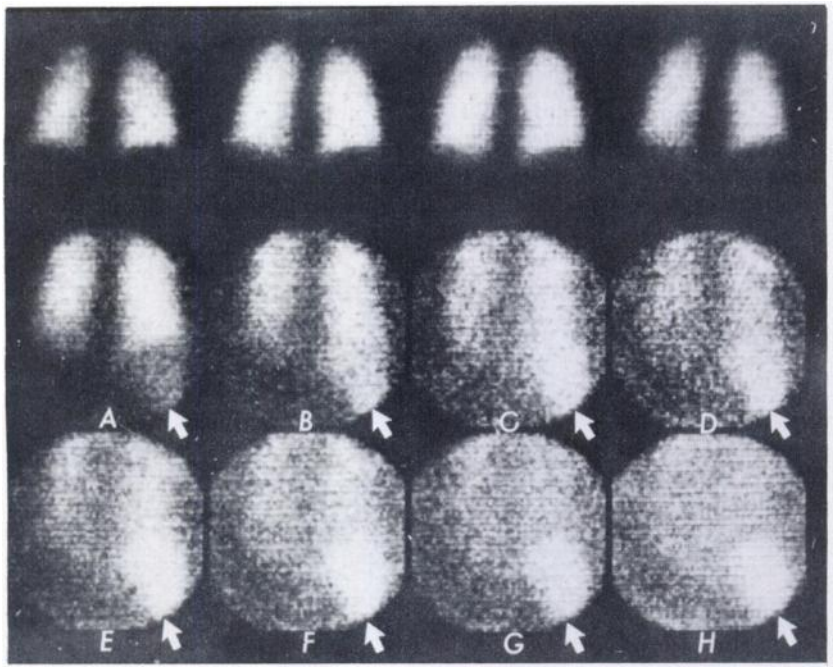

FIG. 1. Radioxenon ventilation study. Top row of scintiscans represent radioxenon inhalation phase to point of equilibrium. Each scintiscan represents 1-min of accumulation. Washout of radioxenon begins at scintiscan A. Scintiscans A–D occur at 30-sec intervals, E–G at 60-sec intervals, and H represents a 150-sec interval. Total time represented is 11.5 min. Accumulation and retention of radioxenon in liver is indicated by arrows. This study would be graded as 4+ for hepatic radioxenon accumulation and retention.

United States the most common cause of hepatomegaly is alcohol-induced fatty liver (*11*). The true incidence is probably not known because of the unavailability of a simple noninvasive diagnostic test. A simple screening procedure is needed not only to detect patients with fatty infiltration but also to increase the diagnostic accuracy of colloid liver imaging, in other infiltrative diseases of the liver with diffuse hepatomegaly, by exclusion of fatty infiltration as a cause.

Alcoholic fatty infiltration of the liver is both preventable and curable. It is associated with a variable symptom complex that may simulate an acute surgical abdomen or obstructive jaundice and produce manifestations of portal hypertension or symptoms of acute hepatic failure. All of these alterations may disappear with removal of liver fat. Continued consumption of alcohol to excess may lead to alcoholic hepatitis and cirrhosis and the increased morbidity and mortality associated with these diseases (*1*).

Sequelae of fatty infiltration make it a major complication of alcoholism, and therefore each alcoholic patient should be investigated for its possible presence. Periodic re-evaluation during treatment will provide an index of the efficacy of the therapy to remove accumulated fat. The results of the present study suggest that hepatic xenon accumulation parallels hepatic lipid content. The preliminary data in humans suggest that hepatic xenon accumulation may indeed indicate fatty liver in man. Further studies are in progress in our laboratory, using chemical, morphologic, and radioisotopic methods to quantitate the acute and chronic relationship between hepatic lipid content and xenon retention in experimental animals. Current studies in humans are being directed toward correlation of hepatic xenon retention with hepatic histology and lipid content, as well as toward development of computerized procedures for the measurement of xenon retention by the liver as a quantitative estimate of hepatic lipid content. Recognition and quantitation of fatty liver by hepatic xenon accumulation may prove to be a useful diagnostic test for screening and followup assessment.

FOOTNOTES

* Searle Radiographics model 4220, Des Plaines, Ill.

† Xenon-133 Lung Function Unit, model 36-001, Nuclear Associates, Inc., New York, N.Y.

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