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# Diagnosis of fatty infiltration of the liver on contrast enhanced CT: limitations of liver-minus-spleen attenuation difference measurements

**R. J. Johnston,**[1] **E. R. Stamm,**[2] **J. M. Lewin,**[2] **R. E. Hendrick,**[2] **P. G. Archer**[3]

[1]Department of Radiology, Veterans Affairs Medical Center, Stop 114, 1055 Clermont Street, Denver, CO 80220, USA
[2]Department of Radiology, Box C277, University of Colorado Health Sciences Center, 4200 E. 9th Avenue, Denver, CO 80262, USA
[3]Department of Preventive Medicine and Biometrics, Box B119, University of Colorado Health Sciences Center, 4200 E. 9th Avenue, Denver, CO 80262, USA

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**Abstract**
*Background:* We investigated whether liver-minus-spleen (L-S) attenuation differences can accurately diagnose fatty infiltration of the liver on contrast-enhanced computed tomography (CT).
*Methods:* A group of 78 patients administered a fast injection (90-s duration) of 150 mL 60% ionic contrast was compared with 81 patients given a slow injection (152.5 s). The presence or absence of fatty infiltration of the liver was diagnosed by noncontrast CT.
*Results:* The L-S attenuation differences varied significantly, depending on both injection rate and timing of measurements. For the fast-injection group, the optimal L-S threshold for diagnosing fatty infiltration ranged from −43 to −33 Hounsfield units (HU) for early (79 s) and late measurements (106 s), respectively. For the slow-injection group, the optimal threshold ranged from −31 to −25 HU (80 and 112 s, respectively). In addition, sensitivity was not very high (range = 0.54–0.71) for either injection protocol at any measurement time because of significant overlap of L-S values between normal and fatty infiltration patients. Moderate and severe fatty infiltration were more reliably diagnosed than mild fatty infiltration by this method.
*Conclusions:* Contrast injection rate and timing of measurements significantly influence the optimal L-S threshold for diagnosing fatty liver. This limits the clinical usefulness of such measurements.

*Correspondence to:* R. J. Johnston

**Key words:** Computed tomography, contrast media—Computed tomography, tissue characterization—Liver, CT—Liver, diseases—Liver, fatty.

Computed tomography (CT) has been widely employed in the diagnosis of fatty infiltration of the liver. Liver density as measured by CT attenuation units on noncontrast CT (NCCT) has been shown to be related in an inverse-linear fashion to the degree of fatty infiltration [1–3]. Unfortunately, measurement of absolute liver attenuation to diagnose fatty infiltration has proven impractical because of wide interpatient and interscanner variation in liver CT attenuation values. However, fatty infiltration can be reliably diagnosed on NCCT by recognition of a lower attenuation for the liver than the spleen [4–6].

Whether this method for diagnosing fatty infiltration of the liver can be extrapolated to contrast-enhanced CT (CECT) is an important question because liver CT is now routinely performed without a preliminary noncontrast study. The spleen usually has greater enhancement than the liver when scanned during the most optimal phase of liver imaging [7–9]. Thus, on CECT the diagnosis of fatty infiltration by simple comparison of liver and spleen attenuation is not straightforward, and a different diagnostic threshold is needed. The purpose of this study was to evaluate whether a specific threshold of liver-minus-spleen (L-S) attenuation difference can accurately diagnose diffuse fatty infiltration of the liver during contrast enhancement and whether this threshold is affected by contrast injection rate and measurement timing.

## Materials and methods

A total of 159 CT studies in 153 patients were prospectively evaluated. Patients with poor intravenous access, serum creatinine level greater than 2.0 mg/dL, vomiting or other interruption during scanning, excessive motion or streak artifacts, or who required nonionic contrast or a special scan technique (e.g., thin cuts) were excluded. All studies were performed on one of two Picker 1200 CT scanners (Picker International, Highland Heights, OH) at two hospitals, with a 3.4-s scan time, 4.5-s average interscan delay, and an average of 7.6 scans per minute. Both machines allowed 12–14 scans before heat loading of the X-ray tube, which was usually adequate to cover the liver during the optimal enhancement phase.

For each study, three or four preliminary 10-mm-thick NCCT slices were obtained through the liver and spleen at 20–30-mm intervals. An automated injector (Medrad, Pittsburgh, PA) was then used to deliver 150 mL of 60% diatrizoate or iothalamate meglumine (42.3 g iodine) intravenously. One of two protocols was used. Group 1 included the first 78 studies and utilized a fast biphasic injection, with a first phase of 60 mL at 2.0 mL/s, followed by a second phase of 90 mL at 1.5 mL/s, for a 90-s total injection time. Group 2 consisted of the subsequent 81 studies and utilized a slower biphasic injection, with a first phase of 60 mL at 1.5 mL/s, followed by a second phase of 90 mL at 0.8 mL/s, for a 152.5-s injection time. Both protocols used a 30-s delay after the start of injection before the onset of scanning. Images 10 mm thick were then obtained from the diaphragm through the liver, with breathing between each slice. Both groups were well matched in age, sex, and distribution of patients between the two hospitals.

Liver and spleen attenuation measurements in Hounsfield units (HU) were obtained by using at least three individual slices from both the noncontrast and contrast-enhanced portions of each study. For each slice, at least three separate 1.0-$cm^2$ region-of-interest (ROI) measurements were averaged for both the liver and spleen. To avoid partial-volume averaging effects, care was taken to avoid measurements from vessels, focal lesions, areas of artifact, or near the edge of organs. In addition, only measurements from the posterior two-thirds of the right liver lobe were made because this region is similar to the spleen in anatomic location, with resultant similar artifacts, and we observed that attenuation values from the left lobe were consistently higher than those from the right lobe. This observation has been confirmed by others [10]. In the two patients who had fatty infiltration confined to a lobar or segmental liver region, measurements were obtained only from the abnormal region. Liver and spleen attenuation measurements and L-S attenuation differences were computed for each measured slice and then averaged over all measured levels to calculate the mean measurement for each patient. The delay time after the start of injection was also determined for each measured slice.

The medical records of all patients were meticulously reviewed to identify a subset of normal patients within our population of study patients. Excluded from this subgroup were all patients with hemochromatosis or with risk factors associated with fatty infiltration, including diabetes, cirrhosis, hepatitis, ETOH abuse, severe obesity, ileal-jejunal bypass, TPN, steroids, or significant elevation of serum transaminases. Patients with abnormal or enlarged spleens on CT scans and patients with obvious evidence of diffuse liver disease were also excluded. Only 80 of the 159 studies met these strict criteria. The range of L-S attenuation differences on NCCT was determined for this normal group. We used 2 SD below the mean of the normal population as a threshold below which there was presumptive evidence of fatty infiltration. The validity of this threshold was established by comparison with prediction intervals from least-squares regression of normal liver and spleen attenuation measurements. Biopsy proof was not obtained.

The optimal threshold for diagnosing fatty liver on CECT was determined by calculating sensitivity, specificity, and accuracy over a range of possible L-S diagnostic thresholds and choosing the L-S value that maximized overall accuracy. This method is reasonable, assuming that the ''cost'' of a false-positive and false-negative diagnosis are relatively equal, in which case a cutoff value can be selected based on minimizing error [11]. Where two threshold values had the same overall accuracy, the lower threshold was chosen to increase sensitivity. This analysis was repeated independently for the first three measured slices and the mean of all slices.

## Results

### *Noncontrast CT in normal patients*

For the 80 patients classified as normal by clinical history, the liver was an average of 8.7 HU higher in attenuation than the spleen on NCCT (SD = 5.5, range = −2.6–21.4). There was a strong linear correlation between liver and spleen attenuation values (R = 0.769, $p < 0.0001$), despite wide variation in liver and spleen attenuation measurements among the normal population (Fig. 1). In this analysis, because the spleen was used as the norm for estimation of liver density, the spleen was treated as the independent variable. The difference between liver and spleen attenuation (L-S) provides an optimal scale for the assessment of normal liver density provided that the slope of the regression line relating the two measurements is 1.0 or close to it. This regression yields a line with slope of 0.912, a value not significantly different from 1.0 (t = 1.255, $p = 0.21$, two-tailed test). Furthermore, our analysis indicated that the distribution of L-S attenuation differences closely resembles a normal (Gaussian) distribution, thus justifying the use of the standard deviation to estimate the boundaries of the normal range. Two standard deviations below the mean L-S attenuation difference is −2.3 HU, and this is the threshold below which we diagnosed fatty infiltration of the liver in our study population. This threshold closely approximates the lower 95% prediction interval about the regression line for the normal population (Fig. 1).

### *CECT: effect of changing injection rate and measurement time*

For patients with no evidence of fatty liver on NCCT, those scanned with the faster contrast injection had a larger mean postcontrast L-S attenuation difference (−15.2 HU) than those given the slower injection (−12.1 HU; Table 1). This difference was statistically significant (t = 2.09, $p < 0.02$). The difference between L-S values for the fast and slow groups was even more pronounced when evaluating the early, first slice measurements (−18.4 and −14.2 HU, respectively), and this was also statistically significant (t = 2.25, $p < 0.02$). In addition, there were distinctly different attenuation versus time profiles for the two injection protocols (Fig. 2).

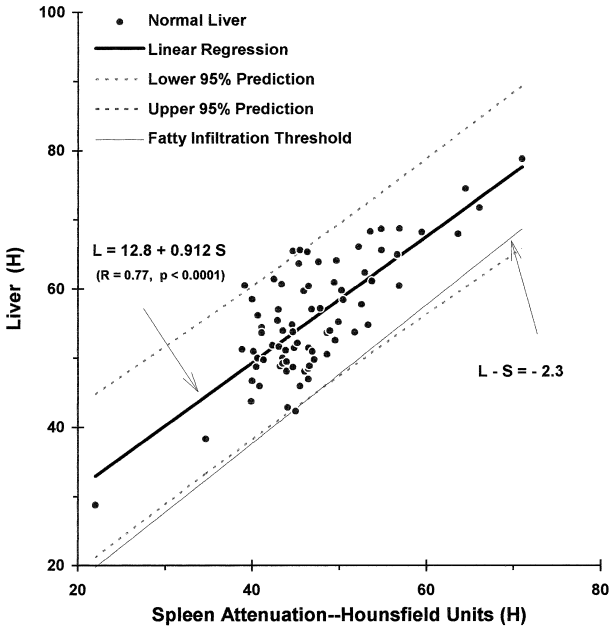


**Fig. 1.** Liver (L) versus spleen (S) attenuation measurements from NCCT scans in normal patients (n = 80). The thick solid line is the best-fit least-squares regression line. The thin solid line is the L-S attenuation difference threshold (−2.3 HU) for diagnosing fatty infiltration of the liver, which closely approximates the lower 95% prediction interval (dashed line) about the regression line.

The fast-injection liver and spleen curves reached distinctive early peaks followed by a steady drop in attenuation values, whereas the slow injection resulted in a slower progressive increase in both curves, indicating later peaks of lower attenuation than those from the fast-injection group. For both groups, spleen enhancement rose more rapidly than liver enhancement, resulting in peak L-S attenuation differences during the early measurements. During later measurements (120–180 s), L-S attenuation values rapidly diminished in the fast-injection group but stabilized at a near-steady state in the slow-injection group. The large distribution of values about the mean indicates wide interpatient variation underlying these trends, which was more pronounced at the faster injection rate.

### *Fatty infiltration: accuracy of diagnosis on CECT*

Twelve of 78 patients in the fast-injection group and 19 of 81 patients in the slow-injection group had fatty infiltration of the liver, as determined by noncontrast L-S values lower than −2.3 HU. Following contrast enhancement, mean L-S attenuation difference measurements demonstrated significant overlap between patients with and without fatty infiltration (Fig. 3). For example, in the fast-injection group, the mean postcontrast L-S attenuation difference range was −93.0 to −14.9 in patients with fatty infiltration and −51.7 to 7.1 in patients without fatty infiltration. There was comparable overlap in the slow-injection group (−115.0 to −7.4 fatty; −30.0 to −0.6 nonfatty). We observed similar overlap when evaluating time-categorized (individual slice) measurements for both the fast- and slow-injection groups.

The optimal threshold for diagnosing fatty liver was significantly different for the two injection protocols and also demonstrated significant time dependence

**Table 1.** Effect of fast and slow injection rates on contrast enhancement of the liver and spleen at different times after injection in patients with and without fatty infiltration of the liver

| | | Nonfatty liver (HU[a]) | | | Fatty infiltration (HU) | | |
|---|---|---|---|---|---|---|---|
| | Measurement time, mean (s) | Liver | Spleen | L-S[a] | Liver | Spleen | L-S |
| Fast injection rate (90 s)[b] | | | n = 66 | | | n = 12 | |
| Precontrast[c] | | 55.2 (7) | 47.8 (5) | 7.4 (5.7) | 32.3 (16) | 47.1 (6) | −14.8 (14) |
| Postcontrast[c] | | | | | | | |
| 1st slice | 79 (14) | 92.7 | 111.1 | −18.4 (12) | 66.9 | 112.1 | −45.2 (23) |
| 2nd slice | 90 (14) | 96.4 | 112.9 | −16.5 (11) | 74.5 | 114.8 | −40.3 (25) |
| 3rd slice | 106 (20) | 100.8 | 112.6 | −11.8 (11) | 76.4 | 112.4 | −36.0 (21) |
| Mean of all slices | 93 | 96.8 (15) | 112.1 (15) | −15.2 (9.9) | 73.1 (23) | 112.8 (13) | −39.7 (21) |
| Slow injection rate (152.5 s)[b] | | | n = 62 | | | n = 19 | |
| Precontrast[c] | | 52.4 (6) | 44.3 (5) | 8.1 (5.8) | 28.0 (17) | 43.9 (4) | −15.9 (16) |
| Postcontrast[c] | | | | | | | |
| 1st slice | 80 (11) | 77.8 | 92.0 | −14.2 (9) | 49.6 | 86.1 | −36.4 (23) |
| 2nd slice | 95 (16) | 83.8 | 95.3 | −11.5 (10) | 50.5 | 88.8 | −38.3 (23) |
| 3rd slice | 112 (22) | 88.5 | 99.6 | −11.2 (7) | 55.4 | 91.6 | −36.2 (24) |
| Mean of all slices | 97 | 84.0 (11) | 96.0 (12) | −12.1 (6.7) | 52.4 (21) | 89.2 (13) | −36.7 (23) |

[a] HU = Hounsfield units, L-S = liver minus spleen
[b] Duration of biphasic injection of 150 mL of 60% iodinated ionic contrast
[c] Numbers in parentheses in these rows are standard deviations

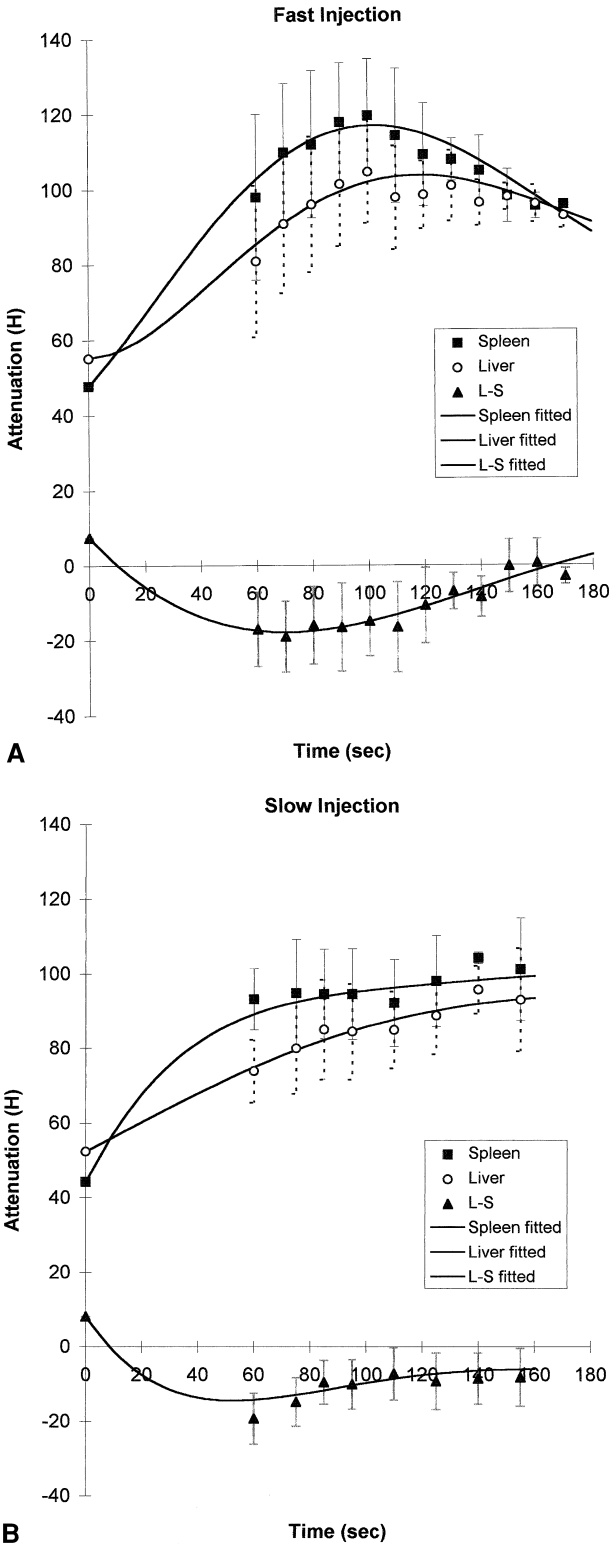


**Fig. 2.** Liver, spleen, and L-S attenuation profiles versus time after the start of contrast enhancement for patients without fatty infiltration. **A** Fast-injection group (90-s injection of 150 mL 60% iodinated contrast). **B** Slow-injection group (152.5-s injection). The error bars included for each data point represent 1 SD from the mean. The solid lines are fifth-order polynomial regression curves fitted to each data series, utilizing the precontrast values as the time = 0 boundary condition.

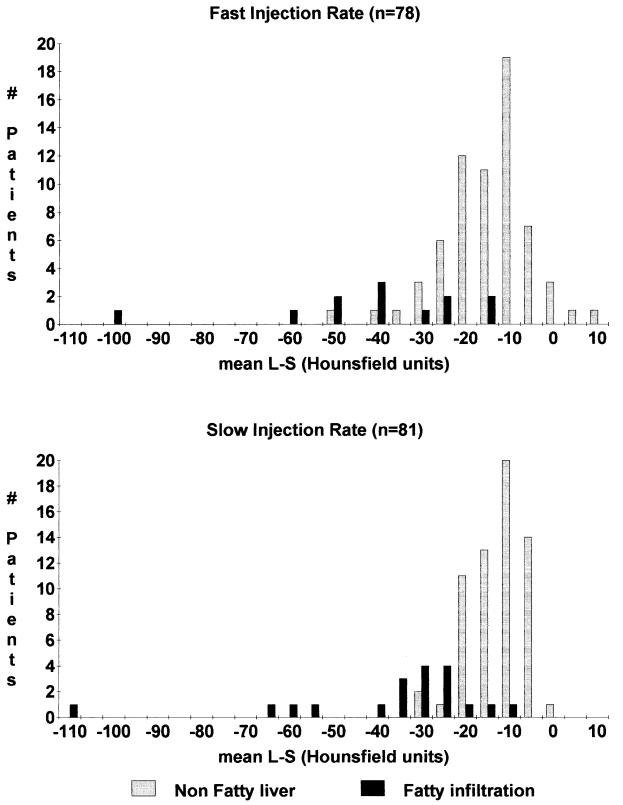


**Fig. 3.** Histograms of mean L-S attenuation differences during contrast enhancement with fast (90 s) and slow (152.5 s) injections of 150 mL 60% contrast. Note overlap in L-S differences between patients with and without fatty infiltration of the liver for both groups.

when considering individual slice measurement times within each protocol (Table 2). For example, in the fast-injection group, the optimal L-S threshold for diagnosing fatty infiltration ranged from −43 to −33 HU for the early (79 s) and late (106 s) slice measurements, respectively. For the slow-injection group, the optimal threshold ranged from −31 to −25 HU (80 and 112 s, respectively). Because of overlap of L-S attenuation differences between normal and fatty-infiltration patients, sensitivity and positive predictive value were only moderate at the optimal thresholds. Overall accuracy was good at all time intervals because of the high specificity of the diagnostic thresholds and the low prevalence of fatty infiltration in the study population compared with the proportion of normal livers.

At the proposed mean thresholds, four of five false-negative results in the fast-injection group and three of four false-negative results in the slow-injection group had relatively mild fatty infiltration, as defined by liver less than 10 HU lower in attenuation than the spleen on NCCT. Considering only cases with moderate or severe fatty infiltration (liver more than 10 HU lower than the spleen on NCCT), sensitivity of the fast injection mean diagnostic threshold was improved to 83% versus only 33% for cases with mild fatty liver. Similarly, in the

**Table 2.** Effect of two different injection protocols and three different measurement delay times on the optimal liver-minus-spleen (L-S) threshold for diagnosis of fatty infiltration of the liver[a]

| | L-S threshold (HU) | Sensitivity[b] | Specificity[b] | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|
| Fast injection rate[c] | | | | | | |
| 1st slice (79 s) | −43 | 0.58 | 0.99 | 0.88 | 0.93 | 0.92 |
| 2nd slice (90 s) | −38 | 0.53 | 0.97 | 0.74 | 0.92 | 0.90 |
| 3rd slice (106 s) | −33 | 0.58 | 0.95 | 0.68 | 0.93 | 0.89 |
| Mean of all slices | −36 | 0.54 | 0.97 | 0.75 | 0.92 | 0.90 |
| Slow injection rate[d] | | | | | | |
| 1st slice (80 s) | −31 | 0.53 | 0.95 | 0.78 | 0.87 | 0.86 |
| 2nd slice (95 s) | −30 | 0.64 | 0.96 | 0.82 | 0.90 | 0.88 |
| 3rd slice (112 s) | −25 | 0.71 | 0.97 | 0.89 | 0.92 | 0.91 |
| Mean of all slices | −26 | 0.71 | 0.96 | 0.86 | 0.91 | 0.90 |

[a] HU = Hounsfield units, PPV = positive predictive value, NPV = negative predictive value
[b] Values were derived from least-squares regression, which smoothed the raw data
[c] A 90-s biphasic injection of 150 mL 60% iodinated ionic contrast
[d] A 152.5-s biphasic injection of 150 mL 60% iodinated ionic contrast

slow-injection group, sensitivity was 90% for moderate to severe fatty liver but only 67% for mild fatty liver. These observations suggest that L-S attenuation differences are more reliable for diagnosing moderate and severe fatty infiltration on CECT, whereas mild fatty infiltration is poorly discriminated from normal liver by this method.

In general, contrast enhancement exaggerated the attenuation difference between the liver and spleen in fatty infiltration patients. However, this did not always occur, as illustrated by the false negative case in Figure 4.

## Discussion

Fatty infiltration of the liver is often an incidental finding in patients with benign predisposing conditions. However, occasionally fatty infiltration represents important objective evidence of ongoing toxic injury or metabolic liver disease such as that caused by alcohol or viral hepatitis, in which case recognition by CT provides clinically important information. In the present study, we reevaluated both NCCT and CECT quantitative criteria for diagnosing fatty infiltration. We felt it necessary to reevaluate NCCT diagnostic criteria because these were used as the basis for diagnosing fatty infiltration.

Our finding that normal liver attenuation was an average of 8.7 HU higher than the spleen on NCCT is similar to values reported by others [9, 12]. The strong linear correlation we demonstrated between noncontrast liver and spleen attenuation values clarifies the observations of Piekarski et al. [4] and justifies the use of the spleen as an internal norm for evaluating liver density. We have demonstrated that a liver attenuation 2.3 HU below that of the spleen provides a reasonable estimate of the lower limit of normal liver density in our patient population. This degree of difference is so close to equality that visual inspection alone should be fairly accurate in confirming normal liver density on NCCT.

Our study has shown that the spleen usually enhances more than the liver during the early phases of contrast enhancement, resulting in predominantly negative L-S attenuation differences—the opposite of NCCT. Two anatomic factors may explain this effect. First, the spleen has relatively higher arterial vascularity than the liver. Second, liver perfusion is dual and predominantly of portal vein rather than systemic arterial origin, unlike the spleen, which has a purely systemic blood supply. Because portal blood must first circulate through the mesentery, peak liver enhancement is delayed and diluted when compared with the spleen.

In addition, we have demonstrated injection-protocol and time-dependent variability in measured L-S attenuation differences. We are unaware of any prior scientific study that has specifically evaluated the relationship of these variables to L-S attenuation differences. Furthermore, we speculate that the more rapid contrast injection rates now commonly utilized with fast, modern, helical CT scanners could result in even more pronounced L-S contrast enhancement differences than those observed in our study. Unfortunately, such a scanner was not available to us at the time of this study.

Most importantly, we have demonstrated that both contrast injection rate and timing of measurements significantly alter the optimal L-S diagnostic threshold for diagnosis of fatty infiltration of the liver. The clinical usefulness of such a threshold is therefore limited because the wide variety of injection rates and volumes, scanner speeds, and scan delays used in different radiology departments necessitates a slightly different diagnostic threshold in each situation. In the only paper we could find that has addressed this issue, Alpern et al.

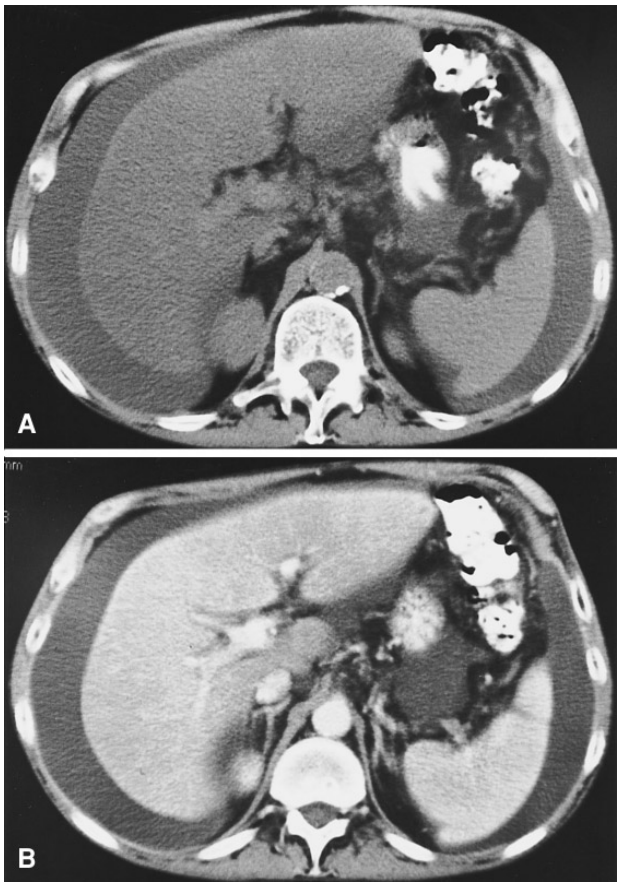


**Fig. 4.** False-negative diagnosis of fatty infiltration after contrast enhancement in a 49-year-old alcoholic with cirrhosis. **A** Preliminary NCCT scan shows liver parenchyma lower in density than portal veins and spleen, indicative of moderate fatty infiltration. Mean precontrast liver, spleen, and L-S attenuation measurements were 23.2, 42.3, and −19.1 HU, respectively. **B** Scan through a similar level approximately 30 s after completion of a 90-s injection of 150 mL 60% diatrizoate meglumine shows no objective evidence of fatty infiltration. Mean postcontrast liver, spleen, and L-S attenuation measurements were 88.1, 103.1, and −14.9 HU, respectively. The postcontrast L-S measurement did not exceed the threshold (−36 HU) for diagnosing fatty infiltration.

found that a confident diagnosis of fatty liver could be made when the spleen-minus-liver attenuation difference exceeded 25 HU after a 2-min injection of 50 g iodinated contrast [9]. However, they did not investigate the effects of different injection protocols or measurement times on the accuracy of their threshold.

Although not studied in the present report, many factors in addition to injection rate influence liver contrast enhancement and probably also affect L-S attenuation difference. These factors include total dose of contrast, body weight, cardiac output, and location of intravenous access [13–19]. Whether the contrast is ionic or nonionic may also affect liver enhancement, although conflicting studies have been reported [19–21]. Splenic enlargement or liver disease are additional variables that can alter the relative perfusion of these organs and change the expected L-S attenuation difference after contrast, as was illustrated by the example in Figure 4.

Given the many variables that affect enhancement, it is not surprising that on CECT we observed significant overlap of measured L-S attenuation differences when comparing patients with and without fatty infiltration of the liver. Mild fatty infiltration was poorly discriminated from normal liver even when using an optimized, injection-rate-specific L-S diagnostic threshold. Moderate and severe fatty liver were more accurately diagnosed by L-S attenuation difference measurements; however, these cases are often easily diagnosed on CECT by subjective evaluation alone. Subjective observation of a pronounced L-S attenuation difference or recognition of additional clues such as ''focal sparing'' [22–25] will likely remain the most practical methods for diagnosing fatty infiltration on CECT. Noncontrast CT is probably a more reliable standard for the detection of fatty infiltration of the liver, and preliminary noncontrast images should be obtained if more accurate diagnosis of fatty liver is an important clinical or research concern.

Potential limitations of this study include the lack of biopsy proof of fatty infiltration, which would be difficult to obtain in any diverse clinical population. Practical considerations required that our fast- and slow-injection rate data were obtained from two different groups of patients rather than from the same group, which would have carried greater statistical weight.

In conclusion, variations in contrast injection rate and measurement timing significantly affect the relative attenuation difference between the liver and spleen (L-S) and alter the optimal L-S threshold for diagnosing fatty liver. Because of these variables and the significant overlap observed between normal and fatty infiltration patients, the usefulness of such L-S attenuation difference measurements for the diagnosis of fatty infiltration on CECT is limited.

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