Original Contribution

IN-VIVO MEASUREMENTS OF ULTRASOUND ATTENUATION IN NORMAL OR DISEASED LIVER

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Abstract—Ultrasonic attenuation coefficients of liver have been derived from echoes received by a modified commercial B-scan imaging instrument. Values have been measured from selected regions within liver scans of 59 individuals, of which 15 cases were presumed normal (based on medical histories), and the remainder were involved with diffuse liver disease such as alcoholic cirrhosis, chemotherapy toxicity, chronic hepatitis, and liver metastases. Medical histories on most individuals include the results of serum liver function enzymes, conventional B-scan examinations, and exposure to drugs and alcohol. The results of CT abdominal scans (N = 13) and/or liver biopsy (N = 12) were also available. The results show that normal attenuation values for human liver are 0.054 ± 0.009 Np/cm-MHz (0.47 dB/cm-MHz) with a frequency dependence of f^n, where n = 1.05 ± 0.25, in agreement with in vitro studies of mammalian liver. In diffuse liver disease, no relationship was found between the attenuation coefficient and the results of CT or conventional ultrasonic examination. A trend towards higher attenuation with increased fibrosis and fat, as graded from liver biopsies, was noted, but the results were generally not statistically significant. However, a significant correlation was found between high values of attenuation and abnormal liver function tests. High attenuation is also found with ingestion of alcohol, chemotherapeutic agents, and steroids, all of which may affect liver composition.

Key Words: Acoustics, Ultrasound, Ultrasonic attenuation, liver disease, tissue characterization.

INTRODUCTION

The attenuation of ultrasound in tissues is an important parameter in many respects. As a measure of loss per propagation distance, the attenuation coefficient at any frequency governs the penetration depth of ultrasound, and thereby acts as a limiting factor for imaging deep organs. The magnitude and frequency dependence of attenuation is a complicated function of the composition (collagen, fat, water) and biochemical environment of an organ (Dunn et al., 1969; Kremkau and Carstensen, 1972; Goss et al., 1980), thus forming a potential basis for tissue characterization. In laboratory studies of myocardial infarcts (O'Donnell et al., 1979) and carbon tetrachloride liver toxicity (Parker and Tuthill, 1986), changes in attenuation have been measured as a function of time as gross changes in tissue composition and function occurred. Clinical measurements of attenuation are more difficult to obtain because of the presence of overlying tissues and the lack of simple transmission paths through uniform regions of the target tissue. Nonetheless, many strategies exist for estimating attenuation using backscattered signals obtained by conventional imaging instruments (Parker and Waag, 1983; Parker et al., 1984; Leeman et al., 1984). The most widely considered class of estimators assume that attenuation increases linearly with frequency, then derive an attenuation slope parameter β, which presumably describes the tissue (Lizzi and Coleman, 1977; Kuc and Schwartz, 1979; Kuc, 1985). Unfortunately, the frequency dependence of attenuation departs from linear in a variety of normal and diseased tissues (Parker and Tuthill, 1986; Naryana et al., 1984; Goss et al., 1979), and small deviations from the linear-with-frequency assumption will produce significant errors in estimators (Naryana and Ophir, 1983).

We have developed a different approach (Parker and Waag, 1983; Parker et al., 1984), where the aver-
age magnitude of backscattered pressure at a discrete frequency is calculated as a function of depth. The decay rate yields the attenuation coefficient at the particular frequency. Thus, by estimating the attenuation coefficients at different frequencies within the bandwidth of the imaging system, the frequency dependence of attenuation can be determined and fit to a convenient description such as a power law fit, \( a_0 f^n \), where \( a_0 \) describes the magnitude and \( n \) the frequency dependence of attenuation within the bandwidth.

Previous studies on tissue equivalent phantoms, where independent measurements of attenuation were available, demonstrated that our technique is both accurate (providing unbiased estimates of attenuation) and precise (with uncertainties of \( \pm 10\% \) for any individual estimate of attenuation at a discrete frequency) (Parker and Waag, 1983; Parker, 1986). Preliminary studies on a small population demonstrated that the two parameter power law fit of the data may provide a more useful discrimination of tissue types than could be obtained by using a single parameter such as the attenuation magnitude at the center frequency (Parker et al., 1984). In this study, the magnitude and frequency dependence of attenuation within normal and diseased livers is given for a larger group of 39 individuals. The analyses show that a number of mechanisms may influence attenuation in vivo, and also demonstrate the ability to provide information which is not available from the conventional B-scan image.

**METHODS AND MATERIALS**

*Population data*

Normal or control values of attenuation were obtained from 15 healthy, nonobese male volunteers ranging in ages from 22 to 41, from whom informed consent (approved by the Committee on Human Experimentation) was obtained. Nine cases were evaluated in 1983 and have been reported in a previous study (Parker et al., 1984). Six additional volunteers were examined in late 1984 for the current study. All normals were in good general health, and had a history of minimal alcohol use and no medications which could be considered to significantly affect liver function or composition.

In-patients and out-patients at the University of Rochester Strong Memorial Hospital were referred to the Department of Radiology for liver ultrasound examination when a preliminary diagnosis such as alcoholic liver disease, presumed chemotherapy induced effects, widespread metastases, or fatty infiltration indicated suitability for this study of attenuation. During 1984 and 1985, 44 cases were examined. Informed consent was obtained, and patient ages ranged from 2 to 84 years.

The conventional ultrasound B-scan image was evaluated by radiologists (M.S.A. and R.M.L.) before attenuation measurements were calculated. Accordingly, the livers were categorized as appearing: normal in size, shape, and echogenicity; or as being enlarged with normal echogenicity; or as having abnormal echogenicity (hyper- or hypo-echoic or multiple lesions evident).

Biochemical liver function tests (LFT) results were available on 39 out of 44 patients. These included serum bilirubin, aspartate aminotransferase, lactic dehydrogenase, and alkaline phosphatase values which were compared against commonly accepted normal ranges (SMA12). Results were summarized as having: no LFT tests available; all values within normal range; or one or more abnormal values. No LFT tests were performed on healthy volunteers but normal values were assumed.

Abdominal CT scans had been obtained and evaluated, independent of this study, on 13 out of 44 patients. These results were encoded in a manner similar to those of the ultrasonic examination, as showing: normal liver size, shape and x-ray attenuation; enlarged liver with normal x-ray attenuation; or abnormal x-ray attenuation and/or multiple lesions evident. No CT scans were obtained from healthy volunteers, but normal results were assumed.

Clinical history of drug use was examined for possible effect on attenuation coefficients. Results were categorized as: no medications or none thought to significantly affect liver function or composition; or recent history of alcohol abuse, anticancer chemotherapy or steroids.

Liver-biopsies were performed, independent of this study, on 12 individuals. Results were evaluated by a pathologist (E.M.S.) and encoded as having: no increase or slight increase in connective tissue; cirrhosis or fibrosis with moderate increase in connective tissue; cirrhosis or fibrosis with marked increase in connective tissue; or mainly inflammatory response, no fibrosis.

The biopsy specimens were also evaluated for fat content and encoded as having: normal fat content, slightly increased fat content, and moderately increased fat content. None of the biopsy specimens exhibited severe fat infiltration. No biopsies were performed on healthy volunteers, where normal tissue was assumed.

In addition to the parameters mentioned above a summary diagnosis class was alternatively applied to all cases, based on the sum of information available excluding attenuation results. The general diagnosis classes were: normal volunteer, 1984 to 1985 study;
normal volunteers, 1983 study; extensive liver metastases from a variety of primary tumors (mainly breast and colon cancer); liver abnormality from chemotherapeutic agents; alcoholic cirrhosis; or all other diffuse liver diseases such as chronic active hepatitis, fatty infiltration and others for which small numbers were available or no clear diagnoses could be made.

Signal processing

Ultrasound echoes were collected by a modified Octoson (Ausonics, Inc., New Berlin, WI) B-scan imaging instrument which has a center frequency of 2.5 MHz and a useable bandwidth of approximately 1 MHz. During each scan, RF waveforms from a single transducer were digitized at a 10 MHz sampling rate, and were stored with positional information and time-varying gain settings. Regions of interest approximately 4 cm transverse by 5 cm axial were selected from regions of uniform illumination and speckle density, avoiding large specular reflectors and other artifacts such as reverberations. Between 80 and 128 waveforms of 750 digitized samples each were thereby used to determine the decay of backscattered pressure as a function of depth and frequency. The signal processing details have been described previously (Parker and Waag, 1983; Parker et al., 1984) and will be summarized below.

The digitized signal was corrected for the non-linear amplifier characteristics, TGC settings, and also for the effects of beam focusing. Segmenting of data as a function of depth was performed by 128 point Blackman windows with 50% overlap. Discrete Fourier transforms were used to determine the harmonic content, thus at any frequency, the average amplitude could be calculated for all depth segments. Least squares estimates of the exponential amplitude decay with depth were then performed, and this yielded the attenuation coefficient (accounting for round trip distance) for 15 discrete frequencies between 2 and 3 MHz. In all but two cases, multiple regions of interest within the same tissue were obtained, by moving the transducer 5-10 mm out of the original plane and re-scanning, or by re-scanning orthogonal to the original plane, or by selecting neighboring regions within a larger, homogeneous area of the liver. The average of attenuation coefficients from up to nine regions of interest were then determined and the resulting values of average attenuation as a function of frequency were curve fit to a power-law function \( a_0 f^n \), yielding a two-parameter characterization of the results.

Alternatively, a more precise single parameter was obtained by evaluating the magnitude of attenuation at the center frequency, 2.5 MHz, using the power-law fit of attenuation values over the entire bandwidth; i.e. \( a_{2.5} = a_0(2.5)^n \). To normalize the attenuation coefficient with respect to frequency, and facilitate comparison with other values in the literature (including measurement of attenuation slope), we report this value divided by 2.5 MHz. Thus normalized attenuation \( a_{2.5}/2.5 = a_0(2.5)^{n-1} \) Np/cm-MHz.

Error analysis

A detailed analysis of uncertainties in attenuation measurement system has been given elsewhere (Parker, 1986), and the results will be summarized herein. The random nature of speckle patterns underlie the uncertainties in calculating attenuation, since the coefficient must be estimated from a noisy exponential decay. For our system (1 MHz bandwidth, 2.5 MHz center frequency, 4 × 5 cm region of interest), it has been shown that the uncertainties in estimating attenuation coefficients at each of 15 discrete frequencies between 2 and 3 MHz is approximately ±10%. The power law fit over this frequency range, given this uncertainty, yields estimates of \( a_0 \) and \( n \) which have approximately ±20% error. However, the normalized attenuation value has a much lower error of ±3% since it is an average of attenuation coefficients within the bandwidth, assuming only a general power law relation between attenuation and frequency (Parker, 1986).

In addition, all the above uncertainties are reduced by averaging results from independent regions of interest within the tissue. In all but two cases, between two and nine regions of interest were used to obtain attenuation estimates, reducing uncertainties by an additional factor of \( N^{1/2} \), or in our case, 1.4 to 3.

In evaluating estimates of attenuation from this study, the correlation coefficient, a measure of the fit of data to theoretical curves was used. If the correlation coefficient was lower than 0.90 for the exponential decay of pressure with depth, or for a power law fit of attenuation, then analysis for a region of interest was rejected. Before averaging results from multiple regions of interest, within a homogeneous area of liver, the scatter of individual estimates of \( a_0 \) and \( n \) were compared to a theoretical distribution (Parker, 1986). Outliers were excluded from averaging of results if the values yielded a normalized attenuation value at 2.5 MHz that was more than ±20% different from the group average. In our experience outliers most often result from nonstationary echo statistics within regions of interest. For example, a barely resolvable artery in a speckle region may be hard to discern from the log compressed B-scan image. However, the strong reflector can cause the pressure versus depth data to deviate from the exponential decay model.
RESULTS

Attenuation values from different patient groups were compared to assess attenuation as a means for tissue characterization. As expected, a Student's t-test on normalized attenuation showed no significant difference between normals measured in 1983 and 1984. Grouped together, the normals had an average normalized attenuation value of 0.054 Np/cm-MHz (range 0.043–0.073 Np/cm-MHz). Cases of widespread liver metastases had average normalized attenuation values of 0.060 (range 0.030–0.081); chemotherapy toxicity 0.087 (range 0.082–0.090); alcoholic liver disease 0.078 (range 0.062–0.092); and the general category of other diffuse diseases 0.071 (range 0.043–0.104).

An analysis of variance and Student–Newman–Keuls test showed a significant difference (p < 0.001) between the following diagnostic categories: those with alcoholic liver disease and other diffuse disease had high attenuation compared to either normals or those with liver metastases. The two patients with suspected hepatic chemotherapy toxicity also had high attenuation values compared to normals, but were not included in the statistical comparisons, because of the small population size (N = 2).

No significant differences in attenuation were found when the population was divided into normal and abnormal based on the results from CT, or B-scan image evaluation. A trend to higher attenuation with increased fat or fibrosis on biopsy was noted, but the results were generally not statistically significant. However, a significant difference was found between normal and abnormal LFT groups (p < 0.01), where the mean attenuation values were 0.057 (range 0.042–0.080) and 0.071 (range 0.035–0.095), Np/cm-MHz, respectively. Also, when all individuals with normal B-scan examinations were grouped by drug consumption, a significant difference in attenuation coefficients (p < 0.001) was found. Specifically, individuals who had B-scan liver images with normal shape and echogenicity but who had exposure to alcohol, chemotherapy, and steroids such as prednisone had mean attenuation values of 0.079 (range 0.060–0.090) Np/cm-MHz; whereas those with normal B-scan images but without exposure to potentially hepatotoxic drugs had mean attenuation values of 0.056 (range 0.043–0.079) Np/cm-MHz. This comparison in particular demonstrates that meaningful information not evident in the B-scan image can be extracted by the analysis of attenuation.

DISCUSSION

General interpretation of results

To facilitate comparison with known properties of tissue attenuation, Fig. 1 shows power-law parameters for attenuation of substances with a wide range of values such as bile (Naryana et al., 1984) and tendon (Goss et al., 1979) measured in vitro. The dotted lines

![Graph](image-url)
demarcate a range of attenuation \(0.04 \leq (\alpha_{2.5}/2.5) \leq 0.07 \text{ Np/cm-MHz}\) with frequency dependence between 0.8 and 1.3. This range was chosen to represent normal in vitro mammalian liver values (Parker and Tuthill, 1986; Parker, 1983) and the lines are reproduced on all subsequent curves for reference purposes. Some general trends emerge which are consistent with simple mixture rules for attenuation of composite materials. Higher concentrations of tissue collagen and fats tend to increase attenuation, vertically and to the right in \(\alpha\) versus \(n\) space. Conversely, low attenuating fluids such as blood and bile are found below the reference lines. Rat liver attenuation, as a function of time following exposure to carbon tetrachloride, first increases at 5 h (R5), then decreases at 24 h (R24) with respect to controls (NR). Presumably, the marked accumulation of triglycerides at 5 h is responsible for the increase, whereas the onset of gross tissue swelling and necrosis gives rise to lower values at 24 h.

In general, however, complicating factors such as the role of collagen sheets, strong scatterers, and changes in proton-transfer relaxation mechanisms (Bealieu et al., 1982), may prevent simple interpretations of data in terms of simple mixture rules. It is also germane to point out that a dependence of attenuation with frequency to a power law less than one (as measured between 2 and 3 MHz in our system), could be caused by dominant low frequency relaxation mechanisms such as phosphate-protein interaction (Bealieu et al., 1982), or by the presence of micron sized bubbles with resonant frequency in the low megahertz range. The latter phenomenon is more likely to be observed in vitro. Beyond the expected scatter in data, other artifactual mechanisms, such as phase cancellation errors could occasionally be responsible for \(n < 1\), but no correlation with patient abdominal fat thickness, or instrument settings were found when these data were reviewed.

**Attenuation versus summary diagnosis**

The plot of all attenuation measurements as a function of power law parameters is given in Fig. 2. A wide range of magnitude and frequency dependence coefficients are evident. A clearer comparison emerges with a plot of normals, along with individuals diagnosed as having alcoholic liver disease and those with chemotherapy toxicity, as shown in Fig. 3. The cases with alcoholic liver disease have greater attenuation, possibly revealing the influence of fat and/or collagen. Cases with chemotherapy toxicity also had higher than normal attenuation coefficients.

Another comparison between all groups is presented in Fig. 4, where the single parameter, normalized attenuation, is plotted as a function of diagnosis category. The wide range of values found in patients with liver metastases and diffuse liver disease can be easily seen in this representation. Higher attenuation in cases of severe alcoholic cirrhosis has also been noted by King, Lizzi et al. (1985).

**Attenuation versus independent clinical parameters**

Given the large number of cases in the category of general diffuse disease, and the spread of values

![Fig. 2. Scatter plot of attenuation values measured in 59 individuals (4 observations are hidden). The patients were classified as normal, mets = metastatic liver disease, chemo = presumed chemotherapy hepatotoxicity, ETOH = alcoholic liver disease, or other diffuse abnormalities. A wide range of attenuation parameters was obtained for the abnormal livers.](image-url)
observed overall, investigation of possible links between attenuation and other clinical assessments seem warranted. Thus, all diagnosis classes were included in analysis of normalized attenuation sorted by conventional ultrasound B-scan, abdominal CT, biopsy results, LFT values, and drugs and alcohol intake. Analysis of variance showed no statistically significant differences within groups sorted by B-scan image, or CT image. The lack of correlation between ultrasound B-scan image and attenuation is not surprising since an abnormal image could result from the presence of highly echogenic, highly attenuating fat or collagen, or conversely by liver edema or infiltration with low attenuating fluid.

Comparisons of attenuation versus fat or fibrosis on biopsy specimens was difficult because of the lim-
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...nated sample size \( N = 12 \). Trends were noted where increasing attenuation was associated with increased fat and fibrosis, but the results were not statistically significant for fibrosis. In the case of fat, an analysis of variance, Student–Newman–Kuels test showed patients graded as having slight to moderate fatty infiltration \( N = 6, \alpha = 0.074 \pm 0.01 \text{ Np/cm-MHz} \) had a significantly higher attenuation \( p < 0.01 \) than normal volunteers \( N = 15, \alpha = 0.054 \pm 0.009 \text{ Np/cm-MHz} \), but not significantly higher than hospitalized patients whose biopsy results showed normal liver fat \( N = 6, \alpha = 0.066 \pm 0.013 \text{ Np/cm-MHz} \) and no or slight increase in connective tissue. These results strongly suggest that there is at least one additional mechanism or factor, besides fat and fibrosis, which can measurably influence liver attenuation. For example, a simple decrease in the liver water content would increase the attenuation coefficient (Bamber et al., 1981).

Taylor et al. (1986) also found that high attenuation was associated with fatty infiltration, with little dependence of attenuation on fibrosis. However, a quantitative comparison of our absolute numbers with the study of Taylor et al. (1986) is not appropriate because that study did not quantify the pulse bandwidth or beam diffraction effects, and relied on TGC settings and comparisons against phantoms for attenuation estimates.

The normalized attenuation values as a function of LFT results are given in Fig. 5. Despite the overlap of values, a significant difference \( p < 0.01 \) is found between normals and abnormals. The data are also shown in \( a_0 \) versus \( n \) space (Fig. 6) and again, the trend toward higher attenuation with abnormal LFT results is evident. It is possible that a further subdivision of LFT results by bilirubin, alkaline phosphate, and liver-specific enzymes would show subgroupings of attenuation with less spread or overlap with normals.

Normalized attenuation values sorted by a history of alcohol, chemotherapy, or steroid exposure showed no statistically significant difference when all cases, including those with grossly abnormal advanced liver disease, were evaluated. The analysis was then restricted to only those cases where the ultrasound examination was rated as normal, in order to test the ability of attenuation measurements to detect changes not evident on the conventional B-scan image. The normalized attenuation values are shown in Fig. 7 for the subclass of normal B-scan results. In this case, a t-test showed significant difference \( p < 0.001 \) between persons with no liver-affecting medications and those with drug history. Here, the individuals with high alcohol consumption are not identical to the group with diagnosis of alcoholic liver disease. Only two individuals with alcoholic liver disease had normal B-scans and could be included in this comparison. The drugs/normal B-scan group also includes four others with high alcohol consumption but no evidence of alcoholic liver disease, and six

Fig. 5. Normalized attenuation (Np/cm-MHz \( \times 100 \)) for patients grouped by the results of serum liver function tests. Despite the overlap or spread in values, a statistically significant \( p < 0.01 \) difference is found between normal and abnormal groups, the latter having higher attenuation.
cases exposed to chemotherapy or steroids.) The trend towards higher attenuation values with drug exposure is evident in Fig. 7. This suggests that attenuation changes are present before detection using conventional grey scale instruments to estimate backscatter. Our preliminary results on attenuation images (Walach et al., 1986) also demonstrated the potential value of independently plotting backscatter and attenuation.

These data are also plotted in \( \alpha_0 \) versus \( n \) space in Fig. 8. Here the group with drug exposure tends to lie towards the upper left of individuals not taking liver-affecting drugs. This position indicates that some low frequency relaxation mechanisms may be contribu-
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Fig. 8. Same data as Fig. 7 but plotted using two parameter power law fit of attenuation. Here, cases with drug exposure are seen to have higher attenuation, and also lie to the left of those without drug exposure. The relative positions may indicate that some low frequency relaxation mechanism may contribute to the higher attenuation.

The drugs/normal B-scan analyses also demonstrates that increased attenuation can be associated with normal echogenicity. (Relative echogenicity here is judged by the radiologists, based on their instrument settings during examination, and also on internal standards such as kidney/liver echogenicity comparisons.) Other data, such as a case of grossly enlarged liver and spleen, showed significantly lower attenuation in the spleen even though the spleen and liver were isoechic, as directly observed from images of both organs in the same scan plane. These and other data from our study support the contention that backscatter and attenuation are essentially independent and (generally) uncorrelated parameters. This independence has long been inferred through lesion shadowing and echo enhancement (Kremkau and Taylor, 1986). A necessary condition for their independence is that absorption mechanisms must dominate attenuation, with scattering contributing only a few percent to the overall wave attenuation. The dominant contribution of absorption to attenuation has been verified in a number of tissues (Lyons and Parker, 1988). However, Garra et al. (1987) found a strong correlation between increased echogenicity and attenuation in their study. This correlation could be due to the specialized set of abnormalities included in their study, or due to the measurement techniques which included assumptions concerning spectral shape of the pulse, frequency dependence of both attenuation and backscatter, and phantom reference calibrations, none of which are required for the attenuation technique used in this study.

CONCLUSION

Measurements of the magnitude and frequency dependence of ultrasound attenuation can provide information which is not evident from conventional grey scale B-scan images. Furthermore, a two-parameter representation of the magnitude and frequency dependence of attenuation can potentially indicate some dominant mechanisms which can change attenuation from normal values. High values of attenuation were correlated with abnormal liver function tests and a history of alcohol, steroids, and/or chemotherapy use, where fat may be a common pathway. Less useful results were obtained for the correlation of attenuation with metastatic liver disease, where large variations were encountered. Poor correlation was found between high attenuation and biopsy examined for fibrosis and fat, although these comparisons were performed on smaller subsets of the population where medical test results were available.

More clinical and laboratory studies are needed to link the changes in attenuation with functional and compositional changes in tissue. Also, studies of liver changes as a function of time seem warranted, particularly in cases of toxicity from alcohol chemotherapy, or other drugs.

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