Correlation of echographic visualizability of tissue with biological composition and physiological state

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(Received 11 May 1973; revised 30 May 1973)

It is argued that the elastic properties of soft tissues are largely responsible for their echographic visualizability and that these are determined, for the most part, by structural collagen-containing components.

Subject Classification: 16.2, 16.8.

The use of ultrasonic echography as a diagnostic tool is becoming ever more widely accepted as an important modality for obtaining significant diagnostic information. Its noninvasive and nondestructive properties further enhance its usefulness in clinical medicine. It is generally accepted that the ability of ultrasonic echography to visualize directly soft tissue structure is dependent upon partial reflection of acoustic energy at interfaces of contiguous juxtaposed tissues exhibiting different acoustic impedances. Although several investigations have confirmed the existence of differences in acoustic impedances in tissues of different types,[1,2] it appears that little attention has been given to delineating the pertinent biological composition and structure differences of these tissues, their attending physical property differences, and the relation between their composition and structure and their physiological state responsible for the crucial impedance differences. It is felt that such elucidation could only improve the accuracy of diagnostic interpretation, identify the most feasible present and future applications, and possibly provide new schemes by which ultrasound can be employed as a new diagnostic tool.

This letter is an initial report of a study undertaken to examine the pertinent physical properties of selected tissues with the view toward identifying the structures comprising the acoustic impedance inhomogeneities visualized in the associated ultrasonic echograms and determining how these properties depend upon the physiological state.

A plane acoustic wave incident at the boundary of two media is partially reflected back into the first medium and partially transmitted into the second medium. The amplitudes of the reflected and transmitted waves at the interface are governed by the inertial and elastic properties of the media, for the elementary considerations considered herein, and the angle of incidence. For unbounded lossless homogeneous isotropic liquid media, the wave speed is given by $(B/\rho)^{\frac{1}{2}}$, where the density ρ represents the inertial aspect of the medium and the bulk modulus B embodies the elastic properties. The impedance of the medium becomes $(\rho B)^{\frac{1}{2}}$ and, for normal incidence, the relative amplitude of the reflected wave is

$$\frac{p_r}{p_i}=\frac{z_1-z_2}{z_1+z_2}=\frac{(\rho_1 B_1)^{\frac{1}{2}}-(\rho_2 B_2)^{\frac{1}{2}}}{(\rho_1 B_1)^{\frac{1}{2}}+(\rho_2 B_2)^{\frac{1}{2}}},$$

where the subscripts identify the two continguous media. By restricting the discussion to high water content tissues, i.e., the soft tissues, and excluding lung and minearlized tissues, it is possible to state that little variation, viz., of the order of 1% or less, occurs in the density, so that $\rho_1 \simeq \rho_2$ and the above relation can be written as

$$\frac{p_r}{p_i}\simeq\frac{(B_1)^{\frac{1}{2}}-(B_2)^{\frac{1}{2}}}{(B_1)^{\frac{1}{2}}+(B_2)^{\frac{1}{2}}}.$$

It is apparent that the reflection characteristic of these biological media are dependent, for the most part, upon the elastic properties of their components and it is thus a pertinent activity to consider the available information on this topic for the purpose of gaining a more complete understanding of the events attending the use of ultrasound as a diagnostic tool.

Table I lists the static or low-frequency (the only type available) elastic properties of some mammalian tissues and components. Collagenous and elastin fibers are the principle components of the connective tissue intercellular matrix. The mechanical properties of a fibrous matrix depend, in addition to the elastic properties of the component structures, upon the degree of preferred orientation of the high-strength fibrillar component and the volume fraction of these components in the composite.[3] Collagenous fibers exhibit an elastic constant greater, by a factor of about 10^3, than that of other mammalian tissues. The degree

TABLE I. Young's modulus of some biological materials.

Material	E (d/cm^2)	
endothelium	negligible	30, 34
smooth muscle	10^6 to 10^7	31, 32, 33
elastin fibers	3×10^6 to 6×10^6	30, 31
collagenous fibers	10^9	30

of preferred orientation and volume fraction of collagen has been shown to be related directly to the elastic properties of cartilage,[4] vascular tissue,[5,6,7] and organ parenchyma and capsules.[8,9] It thus seems reasonable to consider that the amount of collagenous tissue may be the dominant component determining soft tissue elasticity and hence, acoustic impedance. The relative amplitude of a reflected plane acoustic wave incident at a boundary of two mammalian tissues will therefore be a function of the difference in the elastic properties of the collagenous connective tissue matrix of the tissue comprising the interface. The differences in elastic properties of loose and dense connective tissue, resulting from the differences in collagen content and orientation, determine the faculty with which gross anatomic structures in the abdomen (i.e., capsule walls of the liver, spleen, kidney, and bladder), will be visualized by conventional echographic methods. As a result of their distinct connective tissue stroma, many tissues have a unique characteristic echographic appearance which can be used for soft tissue identification.[10,11]

A study comparing the echographic visualization of excised adult pig liver with excised cat liver showed no echo return from the interior of the cat liver while extensive echoes appeared from within the pig liver under the same experimental conditions.[12] The structure of the cat, human, and pig liver is basically the same, except that in man and cat the connective tissue between the hepatic lobules is poorly developed while in pig this tissue structure is dense and distributed throughout the liver in a regular pattern. Thus the increased echo density in the ultrasonic echogram at the same sensitivity may be ascribed to tissue components of greater stiffness.

If the greatest difference in elasticity occurs at an interface of collagenous and noncollagenous tissue, it is reasonable to expect that the greatest reflected amplitude should occur at these collagenous interfaces. Where the collagenous tissue stroma is characteristically altered by a pathological process, a characteristic alteration in the pattern of reflected acoustic energy, as visualized in acoustic echograms, is to be expected. In general, the presence of diseased tissues is represented acoustically by an alteration from the normally depicted reflecting surfaces.[13] Hepatic cirrhosis, which due to a slow necrosis of the hepatic cells with apparent decreased elasticity, as shown by a decreased acoustic impedance, and their subsequent replacement by a collagenous tissue possessing an increased elasticity, shown by an increased acoustic impedance, provides an example. Cirrhosis of the liver may be accompanied by a three-fold increase in collagen content compared with normal liver tissue.[14] Echographic visualization of liver cirrhosis characteristically depicts a mass of interlacing echoes from the interior of the liver, which normally exhibits little echographic internal structure, except under high sensitivity.[12,15] An increase in echo density of the liver equivalent to an increase in system sensitivity between 2.5 and 6 dB in the normal liver results from this pathology.[16] Various induced pathologies in rat liver (normal mean acoustic impedance 1.53×10^5 g/cm^2 sec) have been shown to result in a decrease in acoustic impedance after ten weeks (mean 1.42×10^5 g/cm^2 sec) in accordance with the cellular degeneration shown by histological examination. By the 15th week, the impedance was greater than normal (mean 1.64×10^5 g/cm^2 sec). Histological examination at this time revealed proliferation of biliary canalucali and fibers and anisocytosis of liver cells. After the 40th week, the mean acoustic impedances of incomplete fibrotic livers was 1.68×10^5 g/cm^2 sec, of complete fibrotic livers 1.72×10^5 g/cm^2 sec, of incomplete cirrhotic livers 1.65×10^5 g/cm^2 sec, of complete . cirrhotic livers 1.63×10^5 g/cm^2 sec, and of carcinomatous livers was 1.64×10^5 g/cm^2 sec.[17] It is seen that the acoustic impedance, and hence the elasticity, of liver is intimately related to histological changes of the liver tissue. Cellular degeneration resulted in decreased acoustic impedance interfaces while an increase in collagenous structures and stroma resulted in increased acoustic impedance interfaces, and it was this increase in acoustic impedance at collagenous interfaces which was visualized in the pig liver, cirrhotic liver, and normal liver with increased facility. Both size and elasticity of collagenous frameworks have been found to possess different values in different physiological states.[18,19]

In the postmenopausal breast the glandular tissue atrophies, leaving dense fibrous connective tissue and increased deposits of fat interlaced with connective tissue. The increase of dense fibrous membranes results in a characteristic increase in echo density from the interior of the postmenopausal breast.[20] The increased deposits of fat decrease the overall elasticity of the tissue, which is shown by an average acoustic velocity decrease of 42 m/sec below that of the premenopausal breast.[21]

Connective tissue undergoes desmoplasia in response to injury and tissue invasion by toxic substances and neoplastic tissue and, as part of the inflammatory response, fibroblasts are stimulated essentially to wall off toxic substances with connective tissue. The onset of cancer in epithelial tissues is associated with a concurrent alteration in the connective tissues of the epithelia.[22] There is a two-fold response by connective tissue to neoplastic invasion.[22–25] Upon neoplastic invasion, the destruction of the adjacent connective tissue by the neoplastic cells occurs with increased fibroblast activity and proliferation of connective tissue in the area surrounding the tumor, so that some cancerous tissues become more fibrous than the normal tissue. The manual detection of these fibrous "lumps" of breast cancer, for example, is still the primary method used in medical diagnosis. This alteration of the connective tissue stroma by cancerous growth results in an alteration in the elastic properties of the tissue,

making possible echographic visualization of the growth. In studies on the human breast, with sensitivity chosen so normal tissue appears as a uniform background, tissue abnormalities can be visualized. Echographic visualization of scirrhous adenocarcinoma presents internal structure within the breast corresponding to the advancing strands and encapsulation of this malignant epithial neoplasm.[13,14] Fibrotic metastatic lymph nodes can also be seen. The characteristic appearance of a fibroadenoma, a benign neoplasm with a proliferation of connective tissue, shows increased echoes from the surrounding breast tissue and few internal echoes.[13,20,26] The increased connective tissue with fibroadenomic invasion of premenopausal breast has been observed as an average increase in acoustic velocity of 30 m/sec over normal premenopausal breast.[21] The appearances of these tumors are due to impedance interfaces resultant from the desmoplastic response of the tissue to both benign and malignant neoplasms. Cystic structures show characteristic echographic patterns, allowing for differentiation from tumorous growth. Cysts due to a homogeneous fluid interior produce no inner echoes, in contrast to the exterior tissue, while the encapsulating collagenous surface of the cyst is sharply defined as a thin uniform boundary.[14,20,27] A solid homogeneous tumor may produce an ultrasonic echogram similar in appearance to a cyst but may be differentiated due to the higher acoustic attenuation and the irregular surface of a solid tumor.

There presently exists some difficulty in differential diagnosis of different pathologies with similar acoustic echographic patterns, for example, between solid benign and malignant tumors.[20] Other investigators have reported similar difficulties in differential diagnosis between cirrhosis and metastatic carcinoma in the liver.[14,15,28,36] The similar acoustic inhomogeneities may be due to the presence of similar collagenous interfaces within the tissue. At an early stage, metastases are more inhomogeneous than surrounding liver tissue and will be represented acoustically as a more or less circular collection of stronger echoes than the surrounding tissue. As the tumor grows, however, the desmoplastic response of the normal tissue to the neoplasm maintains an acoustically inhomogeneous region of high acoustic impedance surrounding the metastase, while the connective tissue degenerates in the center of the tumor, decreasing the acoustic impedance. This results in a doughnut-shaped echo configuration at this stage of development, distinctly different from the interlacing echoes of a cirrhotic liver and resulting from interlacing increased collagenous interfaces, thereby allowing for differential diagnosis at this stage of development. Conversely, as these two pathologies become acoustically differentiable with time, a fibroid, usually acoustically differentiable from the characteristic speckled appearance of a hydatidiform mole, may become acoustically undifferentiable with time from a hydatidiform mole as the fibroid undergoes a myxomatous degeneration (essentially becoming structurally or histologically similar to a hydatidiform mole).[29] The altered echo patterns allowing for detection of these tissue pathologies are due to the alteration in collagenous tissue stroma, and hence in acoustic impedance interfaces, resulting in altered reflection characteristics in the pathological tissue.

Several conclusions can be reached as a result of the recognition that the elastic properties of tissues largely are responsible for the acoustic impedance discontinuities visualized by current echographic methods. The elastic nature of collagenous connective tissue determines that interfaces of collagenous tissue are predominantly visualized in the pertinent acoustic echograms. The magnitude of the echoes received is directly related to the preferred orientation and relative amounts of collagen at the interface. Differential diagnosis, for the kinds of cases considered herein, is dependent upon an alteration in these collagenous interfaces, resulting in an alteration in the normal reflection pattern. Difficulties in differential diagnosis of different pathologies may be due to similar collagenous interfaces within the pathological tissues.

ACKNOWLEDGMENT

The authors acknowledge gratefully the partial support of this study by a grant from the Institute of General Medical Sciences, National Institutes of Health.

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