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● *Review*

A REVIEW OF TISSUE SUBSTITUTES FOR ULTRASOUND IMAGING

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Abstract—The characterization and calibration of ultrasound imaging systems requires tissue-mimicking phantoms with known acoustic properties, dimensions and internal features. Tissue phantoms are available commercially for a range of medical applications. However, commercial phantoms may not be suitable in ultrasound system design or for evaluation of novel imaging techniques. It is often desirable to have the ability to tailor acoustic properties and phantom configurations for specific applications. A multitude of tissue-mimicking materials and phantoms are described in the literature that have been created using a variety of materials and preparation techniques and that have modeled a range of biological systems. This paper reviews ultrasound tissue-mimicking materials and phantom fabrication techniques that have been developed over the past four decades, and describes the benefits and disadvantages of the processes. Both soft tissue and hard tissue substitutes are explored. (E-mail: mculjat@mednet.ucla.edu) **© 2010 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Tissue substitute, Tissue mimicking, Tissue equivalent, Phantom, Soft tissue, Hard tissue.**

INTRODUCTION

Tissue phantoms have been used for characterization and calibration of ultrasound imaging systems since the 1960s. Phantoms are also used to compare the performance of ultrasound systems for training of ultrasound technicians, for comparison to computer models and to assist in the development of new ultrasound transducers, systems or diagnostic techniques. The advantage of phantoms is that idealized tissue models can be constructed with well-defined acoustic properties, dimensions and internal features, thereby simplifying and standardizing the imaging environment.

Phantoms are composed of tissue-mimicking materials, with the majority of phantoms having a simple homogeneous internal structure. Simple or complex targets are sometimes embedded within phantoms to mimic internal structures or to serve as characterization targets. Phantoms that accurately mimic heterogeneous organs or organ systems are often referred to as *anthropomorphic phantoms*. The term *tissue substitute* encompasses both phantoms and tissue-mimicking materials.

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Phantoms and anthropomorphic phantoms are available commercially, mimicking many tissues organs and organ systems. Commercial phantoms range in price from hundreds to thousands of dollars and are often preferred for training and calibration of ultrasound systems. However, commercial phantoms are typically designed for broad markets and specific applications, and are not customizable. For this reason, customized design and fabrication of tissue phantoms is required for more specialized applications requiring tailored properties or dimensions, or when seeking to reduce cost.

This paper reviews many of the materials and techniques used to prepare both soft and hard tissue-mimicking materials and phantoms, focusing primarily on those developed for traditional ultrasound imaging rather than those developed specifically for elasticity imaging (elastography), Doppler (string phantoms) or alternate ultrasound techniques such as high-intensity focused ultrasound (HIFU). Many of the relevant acoustic properties and measurements are first discussed, followed by common materials and preparation techniques used to develop general soft tissue phantoms. The subsequent sections focus on the development of specific soft tissue phantoms and on the materials and techniques used to develop hard tissues phantoms. This paper is intended to allow the ultrasound researcher to better understand the

advantages and disadvantages of various techniques and to select the appropriate approach for their own work.

PHANTOM AND TISSUE PROPERTIES

Tissue substitutes used in ultrasonography must possess acoustic properties near those of the tissues of interest, with the most critical acoustic properties of soft tissue substitutes being the compressional speed of sound, characteristic acoustic impedance, attenuation, backscattering coefficient and nonlinearity parameter (ICRU 1998). The most relevant acoustic properties for hard tissues include the compressional and shear wave speeds of sound, characteristic acoustic impedance and attenuation. Speed of sound, c, is typically determined by time-of-flight measurements through a material of a given thickness, and characteristic acoustic impedance is most often calculated from the product of the speed of sound and the measured density, ρ, of a material. The attenuation coefficient, A, can be measured using through transmission techniques, especially for liquids and low attenuation materials (Madsen et al. 1982). Reflective techniques may be more appropriate for attenuation measurements at high frequencies and for dense solids with high attenuation (Singh et al. 2007). The backscattering coefficient, μ_{bs}, a measure of the differential scattering cross section per unit volume, can be measured by comparing B-mode images between phantoms or with reference materials (ICRU 1998). However, the backscattering coefficient is difficult to measure accurately in most laboratories and therefore is rarely reported in the literature (ICRU 1998). The nonlinearity parameter, B/A, is a measure of the degree to which density in a material changes in response to changes in pressure amplitude (Sehgal et al. 1984). However, the nonlinearity parameter of tissue substitutes is also rarely reported. Nonlinear effects are typically small and therefore difficult to determine using conventional techniques (Shui et al. 2008). Also important for tissue substitutes and phantoms is longevity, or the period of time over which the acoustic and mechanical properties are stable and consistent. Longevity can vary widely, from minutes to permanence, depending on the selected materials and preparation technique. Young's modulus, a measure of stiffness under isotropic conditions, is an elastic property that is critical when investigating phantoms for elasticity imaging. However, Young's modulus is not described widely throughout the literature and therefore is not compared here. Others have provided more thorough discussions of tissue substitutes for elasticity imaging (Hall et al. 1997).

Accurate reporting of acoustic properties is highly dependent on preparation, and handling of tissue substitutes and the inherent dependence of acoustic properties, especially attenuation and backscatter, on frequency require that tissue substitutes mimic tissues over a broad frequency range. Acoustic properties are usually reported at room temperature. However speed of sound and attenuation in particular are highly dependent on temperature, and the temperature dependence varies among each of the tissue substitutes. An additional complication for the design of phantoms is that the acoustic properties of real tissues are not constant among people, or even within a person's body, and therefore the targeted acoustic properties for a given tissue are often quoted differently in the literature. Stiffness coefficients and elastic properties of real tissues are known to be dependent on a number of factors, such as age, health, body location, state (*in vivo*, *ex vivo*), fiber orientation and loading (ICRU 1998; John 2004). It is challenging, if not impossible, to create tissue models that take all of these factors into account. However, the variations among and within real tissues also underscore the importance of phantoms, in that they serve as consistent targets for calibration, ultrasound system testing and training that cannot be provided by human subjects, cadavers or animal models.

SOFT TISSUE-MIMICKING MATERIALS

Soft tissues are composed of muscles, tendons, ligaments, fascia, fat, fibrous tissue, synovial membranes, nerves and blood vessels. Although some soft tissue phantoms have been developed to include many of the components of soft tissues, the majority of tissue substitutes have modeled each tissue as isotropic, homogeneous materials. It is also often desirable to prepare homogeneous tissue substitutes that mimic the broader soft tissue environment rather than individual tissues or groups of tissues; this approach is practical because of the relatively modest acoustic variation among soft tissues (roughly 8% in speed of sound when discounting marrow and tendon [Table 1]). In addition, many tissue substitutes are made using techniques developed for general soft tissue and are subsequently modified to better mimic specific tissue properties. To date, a wide range of soft tissues—in liquid, solid or gel form—have been modeled using a variety of formulations, described next. The acoustic properties of these materials are summarized in Table 2. Tissue-mimicking materials used in commercial phantoms, including hydrogel-based Zerdine (CIRS Inc., Norfolk, CT, USA), a condensed milk–based gel (Gammex RMI, Middleton, WI, USA) and a urethane rubber–based phantom (ATS Labs, St. Paul, MN, USA) are described elsewhere (Browne et al. 2003) and are included in Table 2 for reference.

Water and scanning gels

Water and water-based acoustic scanning gels are the simplest tissue substitutes, with water used as a tissue

Table 1. Acoustic properties of tissues

Material	Velocity (m/s)	Density (kg/m^3)	Attenuation (dB/cm MHz)	Acoustic Impedence (MRayl)	Source
Air	330	1.2	–	0.0004	–
Blood	1584	1060	0.2	1.68	ICRU 1998
Bone, Cortical	3476	1975	6.9	7.38	Hoffmeister et al. 2000
Bone, Trabecular	1886	1055	9.94	1.45	Wear 1999
Brain	1560	1040	0.6	1.62	ICRU 1998
Breast	1510	1020	0.75	1.54	ICRU 1998
Cardiac	1576	1060	0.52	1.67	ICRU 1998
Connective Tissue	1613	1120	1.57	1.81	Mast 2000
Cornea	1586	1076	–	1.71	Mast 2000
Dentin	3800	2900	80	8.0	Kossoff and Sharpe 1966
Enamel	5700	2100	120	16.5	Xu et al. 2000
Fat	1478	950	0.48	1.40	Mast 2000
Liver	1595	1060	0.5	1.69	ICRU 1998
Marrow	1435	–	0.5	–	Clarke et al. 1994
Muscle	1547	1050	1.09	1.62	Mast 2000
Tendon	1670	1100	4.7	1.84	Hoffmeister et al. 1994
Soft tissue (Average)	1561	1043	0.54	1.63	Mast 2000
Water	1480	1000	0.0022	1.48	–

substitute for medical ultrasound measurements and calibration since the early days of medical ultrasound (Robinson and Kossoff 1972). The speed of sound in water is lower than that of soft tissue, but the addition of 7.4% ethanol by mass has been reported to increase the speed of sound to 1540 m/s (Giacomini 1947). However, water is limited by its low attenuation coefficient (0.2 dB/m MHz), relative to soft tissue, and therefore does not accurately mimic the soft tissue environment (Wells 1975). Water and water-based materials are also known to have a strong dependence on temperature, with the speed of sound in water varying as much as 50 m/s over the temperature range between 20–40 °C (ICRU 1998). Despite these limitations, water will continue to be used as a soft tissue substitute because of its ease of use and the prevalence of immersion transducers and test tanks. A mixture of water with glycerin or machine-cutting fluid has also been used widely for blood and bone marrow phantoms, and are described in more detail later.

Acoustic scanning gels, primarily composed of water, are also used as soft tissue substitutes and typically have higher velocities than water. However, because scanning gels are designed to minimize absorption and wave scattering, the attenuation is typically far lower than that of soft tissue. For example, Sonotech SG Acoustic Scanning Gel is specified by the manufacturer to have a speed of sound range of 1518–1574 m/s and an impedance of 1.52–1.60 MRayl (Sonotech 2007). Attenuation data is not available but was reported to be similar to that of water.

Gelatin-based tissue substitutes

Among the earliest tissue-mimicking materials prepared for ultrasound imaging were gelatin-based materials. Gelatin, a homogeneous colloid gel, is primarily derived from collagen in animal tissues. The Madsen group mixed gelatin with varying concentrations of alcohol and uniformly distributed graphite powder, with

Table 2. Acoustic properties of soft tissue substitutes

Material	Velocity (m/s)	Density (kg/m^3)	Attenuation (dB/cm MHz)	Impedence (MRayl)	Source
Agarose-based	1498–1600+	1016–1100	0.04–1.40	1.52–1.76+	Burlew et al. 1980; Madsen et al. 1998; D'souza et al. 2000; Ramnarine et al. 2000
Gelatin-based	1520–1650	1050	0.12–1.5	1.60–1.73	Madsen 1978; Bush and Hill 1983
Magnesium Silicate-based	1458–1520	–	0.85	–	Sheppard and Duck 1982
Oil Gel-based	1480–1580	1040–1060	0.4–1.8	1.54–1.67	Kondo, Kitatuji 2005
Open Cell Foam-based	1540	–	0.46 dB/cm MHz	–	Ophir 1981, Ophir 1984
Polyacrylimide Gel-based	1540	1103	0.7 dB/cm @ 5 MHz	1.7	Zell et al. 2007
Polyuerethane	1468	1130	0.13	1.66	Kondo, Kitatuji 2005
Polyvinyl Alcohol-based	1520–1610	–	0.07 – 0.35	1.60–1.77	Kharine, Manohar 2003
Tofu	1520	1059	0.75	1.61	Wojcik, Szabo 1999
Water–based	1518–1574	1000+	–	1.48–1.60	Giacomini 1947; Sonotech 2006
Condensed Milk-based*	1540	–	0.5	–	Browne et al. 2003
Urethane Rubber*	1460	900	0.5–0.7	1.31	Browne et al. 2003
Zerdine*	1540	–	0.5–0.7	–	Browne et al. 2003

* Commercially available. Provided for reference.

p-methyl and p-propyl benzoic acid used as preservatives against bacterial invasion (Madsen et al. 1978; Burlew et al. 1980). Depending on the concentration of n-propanol in water, a speed of sound between 1520 and 1650 m/s at room temperature could be achieved. By varying the concentration of graphite powder in the gelatin-based compound, therefore adjusting the scattering coefficient, the attenuation coefficient was varied between 0.2 and 1.5 dB/cm at 1 MHz. These materials were reported to have high stability near-room temperature over a period of four months, provided that the samples were stored in a closed container below a layer of distilled water. Reported disadvantages to this technique were instability with temperature variations, susceptibility to microbial invasion and the difficulty in achieving uniform distribution of graphite scatterers as the particles settled during cooling (Ophir 1981).

Another gelatin-based soft tissue substitute was later developed using gelatin and alginate and was reported to have improved stability (Bush and Hill 1983). Bath disinfectants were used to minimize microbial contaminants, and addition of calcium chloride ($CaCl_2$) improved thermal stability up to 25 °C. The material had a speed of sound of 1520 m/s, with the attenuation coefficient varying between 0.12–0.5 dB/cm MHz, with the addition of polyethylene or lipid microspheres. Another related study reported that a dense gelatin-alginate composition could be embedded within the material to provide a distinct inner structure (Bamber and Bush 1996). Although the gelatin-alginate technique reportedly addressed the concerns related to the stability and scatterer uniformity, this technique has not been widely adopted in the literature.

Agarose-based tissue substitutes

Agarose gel–based tissue mimics provide another alternative to the use of graphite powders to achieve sufficient attenuation and scattering properties, as well as improved temperature resistance and particle suspension (Madsen et al. 1998). Agarose-based techniques are the most widely used of the soft tissue substitute preparation techniques described in the literature. The broad use of agarose-based substitutes is a result of their well-characterized performance, the ease of fabrication (the mixture can be heated in a microwave) and the flexibility that the process provides, allowing the incorporation of additional ingredients to achieve a range of acoustic properties.

Agarose is derived from agar, a hydrophilic colloid that is extracted by boiling algae. Typically, water and propanol are mixed at a ratio designed for a targeted speed of sound and heated. Dry, high-purity agarose is then dissolved into the mixture to provide structural rigidity, or improved resistance to change in shape, while improving thermal stability. Evaporated milk is used to increase attenuation and is heated separately and combined with a preservative such as thimerosal and poured into the agarose mixture. The resulting compound congeals to a solid mixture that can be poured into a mold. It is important to note, however, that molds are limited to small volume-to-surface area ratios because the congealing substance forms a solid layer between the liquid product and the air and prevents the remainder of the liquid from congealing in the same manner.

The Madsen group originally developed a recipe that resulted in a speed of sound that ranged between 1498 and 1600 m/s, density between 1016 and 1100 kg/m^2 and an attenuation between 0.04 and 1.40 dB/cm MHz (Burlew et al. 1980). This process was later altered to include evaporated milk, achieving a velocity of 1540 m/s, density of 1030 kg/m^2 and attenuation of 0.1–0.7 dB/cm MHz (Madsen et al. 1998). Many agarose-based tissue substitutes have subsequently been made using this technique, with one study including glass beads to further improve scattering properties (Burlew et al. 1980; Madsen et al. 1998, 2003; D'Souza et al. 2001). Material properties have been reported to remain stable for as long as two and a half years under optimal storage conditions (Madsen et al. 1998). However, in routine laboratory use without careful handling, longevity is often limited to less than one month because of microbial invasion or damage to the delicate structure.

An alternate agar-based technique, incorporated into vascular phantoms, was recently developed as part of a European Commission project (Ramnarine et al. 2001). Water, glycerol, benzalkonium chloride, SiC power and Al_2O_3 powder were mixed with a high-strength agar. Benzalkonium chloride was used to control microbial invasion, Al_2O_3 powder to control attenuation and SiC to vary the backscatter. The speed of sound was reported to be 1541 m/s, the attenuation was 0.5 dB/cm MHz and the density was 1054 kg/m^3. The high-strength agar was reported to provide superior structural rigidity compared with standard agarose-based materials and was well suited for vascular flow phantoms (Ramnarine et al. 2001). A recent multi-institution study found that the speed of sound of these materials increased with temperatures between 22 and 37 °C at a rate of 2.1 m/s/°C, and the attenuation decreased at a rate of 0.005 dB/MHz/°C (Brewin et al. 2008). Frequency dependence and longevity were also explored.

Magnesium silicate–based tissue substitutes

Magnesium silicate is an inorganic substance with a structural form that varies with applied stress. Soft tissue-mimicking materials were created by mixing magnesium silicate with tetrasodium pyrophosphate (an electrolyte needed for the hardening of the gel),

n-propanol (to control the speed of sound), water and either graphite or talcum powder (as scattering agents to vary attenuation) (Sheppard and Duck 1982). The speed of sound was reported to be 1458 m/s and was increased to 1520 m/s with the addition of n-propanol. Attenuation was measured to be 0.85 dB/cm MHz, with a linear dependence on frequency reported when graphite powder was used. Magnesium silicate–based tissue substitutes have the advantage of temperature stability (stable from 0 to 100 °C), resistance to microbial invasion and the ability to reform after needle biopsy procedures (Sheppard and Duck 1982). However, these materials are not self-supportive and therefore cannot be sculpted or molded into predefined shapes.

Oil gel–based tissue substitutes

Oil gel–based tissue substitutes were developed more recently and feature a mixture of propylene glycol, a gelatinizer (Dibenzylidene D Sorbitol) and 10 μm polymethyl methacrylate (PMMA) microspheres (Kondo et al. 2005). The advantage of this technique is that the speed of sound and attenuation increase linearly with the proportion of propylene glycol. Attenuation is further varied by increasing the impregnation of PMMA microspheres. In addition, oil gel–based materials have the advantage of immunity to bacterial infection. The Kondo group has reported speeds of sound of 1480 and 1580 m/s, attenuations of 0.4 and 1.8 dB/cm MHz, and densities of 1040 and 1060 kg/m^3 for the nonimpregnated and impregnated gels, respectively.

Ethylene glycol–based materials have also been explored as tissue substitutes and have found use as acoustic reference materials because of their uniformity and constancy (Dong et al. 1999). However, these materials are not ideally suited as soft tissue substitutes because of their high speed of sound (1659 m/s), density (1110 kg/m^3) and low attenuation (0.078 dB/cm at 2.25 MHz; 0.34 dB/cm at 4.5MHz).

Open cell foam–based tissue substitutes

A soft tissue substitute was developed based on open cell foam (Ophir 1981, 1984; Lerski et al. 1982), which is composed of polyurethane foam and a salt (NaCl) water solution. Variation of acoustic properties was achieved using different foam materials and liquids. Altering the concentration of NaCl changed the speed of sound, therefore allowing the speed to be tailored to the desired range. Ophir reported a speed of sound of 1540 m/s and an attenuation of 0.46 dB/cm MHz (Ophir 1981, 1984). An advantage to this process is that localized zones mimicking tissue pathologies or variations can be created within the material by removing regions of foam before preparation, therefore allowing for the creation of simple inhomogeneous phantoms. However, the attenuation is affected strongly by changes in temperature (4% reduction per °C) and the presence of bubbles in the phantom. Methods to control temperature and allow for proper wetting of the foam were described by Ophir (1981).

Polyacrylamide gel–based tissue substitutes

Polyacrylamide gels are matrix materials commonly used in electrophoresis and are formed by the polymerization of the acrylamide monomer. A 10% polyacrylamide gel was used by Zell et al. (2007) as a soft tissue substitute, and was created by mixing acrylamide:bisacrylamide with water, a Tris/HCl buffer (pH 8.8), tetramethyethylendiamine (TEMED) and ammonium peroxodisulfate. The mixture was stirred and allowed to polymerize at room temperature for 45 minutes. Although the speed of sound (1580 m/s) and impedance (1.7 MRayl) were within an acceptable range for soft tissue, the attenuation was found to be too low (0.7 dB/cm at 5 MHz). Polyacrylamide is also highly toxic and requires special precautions during its preparation (Zell et al. 2007).

Polyurethane tissue substitutes

Polyurethane tissue substitutes have been reported to have low Young's modulus, good elastic recovery and immunity from bacterial invasion (Kondo et al. 2005). A polyurethane gel phantom was produced with a density of 1130 kg/m^3, attenuation of 0.13 dB/cm MHz and speed of sound of 1468 m/s. The acoustic properties of polyurethane were shown to be dependent on molecular structure and weight, and attenuation was shown to increase linearly with both temperature and frequency. However, the molecular design of polyurethane gels is complex, and therefore the standardization of the technique is challenging.

Polyvinyl alcohol–based tissue substitutes

Polyvinyl alcohol (PVA), a synthetic polymer, has recently been adopted as a soft tissue substitute. PVA-based tissue substitutes have the advantage that they have high structural rigidity, indefinite longevity, low cost and they require fewer ingredients compared with the more common agarose-based tissue substitutes (Fromageau et al. 2003; Kharine et al. 2003; Surry et al. 2004).

Preparation of PVA-based tissue substitutes requires freeze-thaw cycles to enhance cross-linking between polymer chains. In one process, a 10%-by-weight solution of PVA in water was frozen and thawed in 12-h cycles to attain the desired acoustic properties, with a speed of sound ranging between 1520 and 1560 m/s, attenuation between 0.07 and 0.28 dB/cm MHz and impedance between 1.60 and 1.70 MRayl (Kharine et al. 2003). A 0.01% solution of sodium azide was used to prevent

microbial invasion. A second process was described, in which dimethyl sulfide (DMSO), a polar aprotic solvent, was added to facilitate structural arrangement in the solution by lowering the freezing point, thereby strengthening the gel (Kharine et al. 2003). Properties achieved using this technique ranged between 1550 and 1610 m/s, 0.34 and 0.35 dB/cm MHz and 1.65 and 1.77 MRayl. Glass can be added to PVA before freezing to increase scattering and to vary the attenuation. The primary disadvantage of PVA-based tissue substitutes is the preparation time, which requires multiple 12-h freeze-thaw cycles and the requirement for precise temperature control.

Silicone polymer–based tissue substitutes

Silicone products have been suggested as potential tissue substitutes because of their longevity, stability, variable Young's modulus and their capacity to be embedded by scatterers such as glass and plastic microspheres. However, these materials are limited by high attenuation and low speed of sound, reported to be $<$1000 m/s (Robertson et al. 1992; ICRU 1998).

Organics

Organic materials have been used as tissue substitutes, including tofu and animal tissues. Tofu has an appropriate speed of sound (1520 m/s), attenuation (0.75 dB/cm MHz) and density (1059 kg/m^3) (Wojcik et al. 1999). Although tofu is low cost and does not require preparation, it has a lower nonlinearity parameter (6.0) than soft tissue (8.0), is susceptible to microbial invasion, its properties cannot be adjusted and its properties vary depending on the brand and preparation. A recent study also found that the attenuation of tofu is highly frequency-dependent, therefore limiting its use at high frequencies (Kim et al. 2009). Porcine tissue, bovine tissue, turkey breast and other animal tissues have been used to mimic human tissue, but they have limited longevity and their acoustic properties cannot be tailored (Davies and Kew 2001; Xu et al. 2005).

SOFT TISSUE PHANTOMS

Many of the soft tissue substitute preparation techniques described before have been modified and tailored to mimic specific tissues or organs. Some have combined multiple techniques to develop phantoms or more realistic anthropomorphic phantoms. A sampling of the techniques used to mimic specific soft tissues and organs are provided.

Blood phantoms

Blood phantoms are used to mimic blood both acoustically and rheologically. Human blood itself has been used in previous studies (Erskine and Ritchie 1985; Weskott 1997) but is limited in its use because of its short lifespan, damage to erythrocytes and change in acoustic properties at room temperature (Oates 1991).

Machine cutting fluid (Syn Cut HD; Acra Tech, Toronto, Ontario, Canada) with distilled water has been reported to be a good blood-mimicking fluid (Frayne et al. 1993; Rickey et al. 1995), with viscosity similar to that of whole blood and cellulose particles added to mimic the backscatter of human blood (Frayne et al. 1993; Rickey et al. 1995). This material was reported to have a speed of sound of 1550 m/s, an attenuation of 0.2 dB/cm MHz and an acoustic impedance of 1.6 MRayl (Frayne et al. 1993; Rickey et al. 1995).

Many additional blood phantoms reported in the literature have been composed of a mixture of glycerol or glycerin and water. Sephadex, a cross-linked dextran gel, mixed with glycerol and water, has been suggested for use as a blood substitute (McDicken 1986; Hoskins et al. 1990; Eriksson et al. 1991) and has been shown to closely mimic blood if its flow is laminar (Mo and Cobbold 1986). Another group developed a blood-mimicking fluid using only glycerin and water (Boote and Zagzebski 1988). The recipe was later modified by adding polystyrene beads to improve the backscatter coefficient, resulting in a speed of sound of 1600 m/s and density of 1040 kg/m^3 (Moehring and Ritcey 1996). Variations of this technique were developed using orgasol (nylon powder; Colombes, France) particles and a surfactant to create backscatter (Oates 1991; Ramnarine et al. 1999; Samavat and Evans 2006; Tortoli et al. 2006), yeast to increase scattering (Ferrara et al. 1996) and cellulose fibers for a backscatter signal comparable to human blood (Petrick et al. 1997).

Bone marrow

Studies that developed bone substitutes have also included bone marrow. Bone marrow substitutes were prepared using materials such as water (Moilanen et al. 2007), butter (Moilanen et al. 2004), a mixture of gelatin and water (Clarke et al. 1994) and vegetable oil (Strelitzki et al. 1996; Strelitzki and Truscott 1998).

Brain phantoms

Because of the comparable acoustic properties between average soft tissue and brain tissue, various soft tissue substitute preparation techniques can be used to create brain phantoms. One group used an agarose-based technique originally developed for prostate phantoms to create a brain phantom that was used for the evaluation of a noninvasive focal brain surgery (Hynynen et al. 2004). Another group used a PVA fabrication process, initially developed for soft tissue, to make an anthropomorphic brain phantom, using a 3-D magnetic resonance image (MRI) to create the phantom mold

(Surry et al. 2004). This technique was later adapted to create a multilayered anthropomorphic brain phantom by combining three different PVA layers and plastic tubing (Reinertsen and Collins 2006).

Breast phantoms

Breast phantoms that closely mimic the attenuation, speed of sound, density and backscatter of breast tissue were produced by the Madsen group in 1982 (Madsen et al. 1982). The process combined oil, gelatin and agar to mimic four layers of tissue, including glandular tissue, adipose tissue, skin and Cooper's ligaments (Fig. 1). The difference in Young's modulus between oil and gelatin was shown to mimic the difference between healthy and abnormal breast tissue *in vivo*. A different technique was used to develop breast elastography phantoms and featured safflower oil dispersed in a solid aqueous gelatin (Madsen et al. 2006b). A good review of breast phantom fabrication techniques was recently published by Madsen et al. (2006a).

Cardiac tissue phantoms

Cardiac ultrasound phantoms have application to ultrasound imaging and color-flow Doppler imaging. One group developed a heart-mimicking phantom from polyurethane or gelatin, portions of a commercial soft tissue phantom and water with embedded 5-μm silica microsphere scatterers mimicking blood (Smith and Rinaldi 1989). This model was later improved by adding a bifurcating aorta and three coronary arteries (Smith et al. 1991).

Eye phantoms

In an effort to determine the biomechanical properties of cornea with high-frequency ultrasound, contact lenses were suspended in 2% agarose (Liu and Roberts 2004). The group described preliminary data in which they simulated acoustic reflections from tissue layers and carried out experimental studies to match the simulations. However, limited details are available.

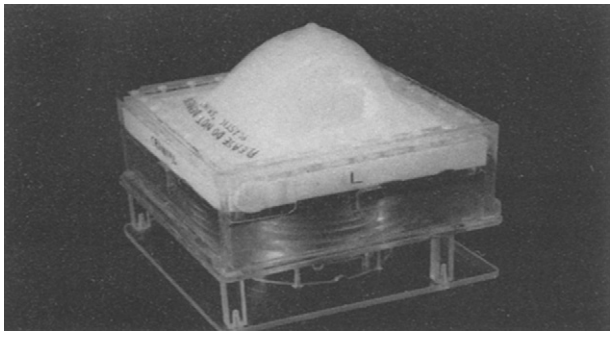

Fig. 1. Breast phantom with oil, gelatin and agar mimicking various layers within the phantom (Madsen et al. 1982).

Liver phantoms

Liver tissue substitutes have been created using several techniques described for general soft tissue. Homogeneous liver phantoms have been made from gelatin and graphite, similar to the Madsen group's 1978 technique, to compare attenuation and echogenicity between healthy and diseased liver (Garra et al. 1987). Condoms filled with water have been used to mimic cancerous and healthy livers in a 3-D ultrasound study (Xu et al. 2003). Liver phantoms created from open cell foam and water have been used in a study comparing echogenic and standard biopsy needles (Hopkins and Bradley 2001). Breast phantoms have also been used to mimic livers during training for ultrasound-guided liver biopsies (Nicotra et al. 1994).

Prostate phantoms

The agarose-based tissue substitute fabrication technique developed by Madsen et al. (1998) was altered to mimic prostate tissue (D'Souza et al. 2001). Agarose-based prostate phantoms were developed that included water, agarose, lipid molecules, proteins, thimerosal and glass beads. The concentrations of agarose and glass beads were increased to increase the attenuation of the material. Several other materials were further added to accommodate MRI, including ethylenediamine tetraacetic acid and Cu^{2+} to control the longitudinal and transverse (T1 and T2, respectively) relaxation times.

Sinus cavity phantoms

Doppler ultrasound has been proposed as a technique to diagnose sinusitis, because the viscosity of sinus fluid is a known indicator of the presence of an infection (Jansson et al. 2005). One group used agar with graphite powder to construct an anthropomorphic sinus phantom using a mold created from a human cranium. Water-glycerol solutions with varying viscosities were used to mimic mucous and serous fluids in the sinus (Jansson et al. 2005). A more recent study by the same group used bovine cortical bone to cover the graphite and agar phantom, and used milk as the fluid mimic (Jönsson et al. 2008). Milk was selected because of the presence of natural scattering particles.

Skeletal muscle phantoms

Skeletal muscle has acoustic properties that are close to those of average soft tissue (Table 1); therefore, many of the general soft tissue substitute formulations can be used to generate materials that mimic skeletal muscle. One group briefly described a skeletal muscle phantom that featured a gelatin-based material (Edmonds et al. 1985) and another described an agarose-based technique for use as a multimodal phantom (D'Souza et al. 2001).

Both techniques treated skeletal muscle as an isotropic material.

Vascular phantoms

A number of techniques have been developed to acoustically model vascular structures, with the majority focusing on large arteries, such as the carotid artery and coronary artery. Vascular phantoms can be grouped into three general categories: basic vascular phantoms with a simple tubular structure; walled vascular phantoms, which have a closer resemblance to the arteries; and wall-less phantoms, which do not have tubing separating the tissue-mimicking and blood-mimicking materials. Real vessels harvested from cadavers have also been used as phantoms in many studies (Kerber and Heilman 1992; Dabrowski et al. 1997, 2001). However, because of their limited longevity and variable geometries and flow patterns, excised vascular tissues are poor models.

Basic vascular phantoms have been made from PVA (Nadkarni et al. 2003; Schaar et al. 2005). A combination of 10% PVA solution with 0.75% enamel paint followed by two freeze-thaw cycles was found to have properties similar to human vascular tissue (Nadkarni et al. 2003). This technique allowed the elasticity to be varied by changing the concentrations of PVA to model both healthy and diseased tissue. Another basic vessel phantom was constructed using latex rubber tubing to mimic the femoral artery, and by mounting the tubing within a gelatin filled frame to mimic the adjacent soft tissue (Zhang and Greenleaf 2006). Another group used a rubber ring with wires attached to the outer surface to provide fiducial markers (Kawase et al. 2007).

Walled vascular phantoms have been built to better understand the onset of vascular diseases using ultrasound. A rigid model of carotid artery bifurcation was created by injecting water-soluble jeweler's wax into an acrylic mold (Bharadvaj et al. 1982). Another group adapted this technique by using lead-cored nylon as fiducial markers, acrylic and high-density polyethylene as a protective housing and layers of agar-based materials to improve visibility of the fiducial markers in the ultrasound image (Frayne et al. 1993). The blood-mimicking fluid was created from machine tool–cutting fluid, as discussed earlier. A later version replaced the agar gels with solid polyester to improve durability but caused beam distortions and artifacts because of an increased impedance mismatch (Smith et al. 1994). In another study examining vascular plaques in the carotid arteries, arterial phantoms were made using an acrylic rod within a box that was filled with a solidified mixture of agar, glycerol, distilled water and sigma cells (Anthony and Aaron 2002; Landry and Fenster 2002). Plaques were created by pouring the same mixture with a reduced concentration of sigma cells into stainless steel molds and embedding the plaques into the acrylic rod. A water and glycerol mixture was used as the blood substitute.

Wall-less vascular phantoms have been used for evaluation of Doppler ultrasound systems. These phantoms are better suited to Doppler flow studies, because image distortion that typically results from tube walls is reduced (Patterson and Foster 1983; Rickey et al. 1995). Homogeneous vascular phantoms were constructed using the European Commission agar-based technique, which also featured water, glycerol, benzalkonium chloride, Al_2O_3 and SiC (Teirlinck et al. 1998; Ramnarine et al. 1999; Tortoli et al. 2006). A mixture of pure water, glycerol, orgasol particles and a surfactant served as the blood mimic (Ramnarine et al. 1999; Tortoli et al. 2006). This phantom was reported to have good longevity and durability to flow (Ramnarine et al. 1999), but the agar-based tissue-mimicking material was subject to splitting at the bifurcation apex (Meagher et al. 2007). To combat this problem, one group replaced the agar material with konjac and carrageenan gels (Fig. 2) (Meagher et al. 2007).

Multi-organ phantoms

Anthropomorphic phantoms have been developed that mimic complete organ systems rather than individual tissues or organs. Madsen et al. (1980) developed a torso section using water-alcohol–based gelatin with n-propanol and various test objects to mimic the kidneys, liver, tumors, cysts and bones. Another group designed a multi-organ phantom for needle guidance training by

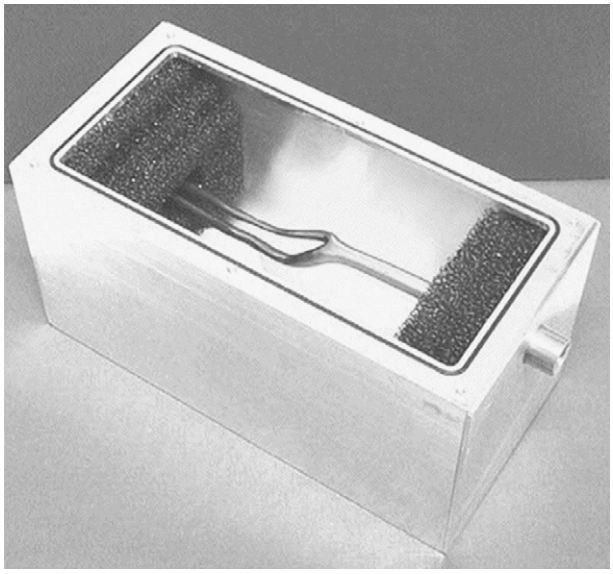

Fig. 2. Low melting point metal alloy core and container used to shape vascular flow phantoms of agar and konjac/carrageenan gel (Meagher et al. 2007). The gel was poured into the container and the metal alloy was melted away by placing the phantom in a hot water and potassium chloride bath.

modeling various organs using balloons filled with degassed water, castor oil and castor clay (Robbins 1985). An adult female pelvis phantom was made using a hydrophilic polymer, water, polyester fiberfill, latex and nylon tubing (Boyce 1993). Rowan and Pederson created a multi-organ phantom using latex to mimic skin, agar and graphite to mimic organs and leaking silicon tubes to simulate internal bleeding as a training tool for the diagnosis of internal trauma (Rowan and Pedersen 2006).

HARD TISSUE-MIMICKING MATERIALS AND PHANTOMS

Hard tissues are mineralized tissues with a firm intercellular substance and include cortical bone, trabecular bone, dental enamel and dentin. Bone substitutes and phantoms have been developed primarily to evaluate and calibrate ultrasound systems designed specifically for detecting bone pathologies (Young et al. 1993; Clarke et al. 1994). Ultrasound imaging of teeth has not yet become clinically accepted, but has been the subject of various studies because of its ability to penetrate hard tissues and its potential as a complement to radiography (Ghorayeb et al. 2008). Dental phantoms have been used to guide the development of dental ultrasound imaging systems (Blodgett 2003; Culjat et al. 2005; Singh et al. 2007). However, because of the higher variation in acoustic properties among hard tissues, it is more challenging to precisely match the acoustic properties using bone phantoms and dental phantoms than with soft tissues. On the other hand, many hard tissue substitutes have greater structural rigidity and longevity than soft tissue phantoms, and therefore are more practical for long-term use. The acoustic properties of hard tissue substitutes are provided in Table 3.

Cortical bone

Cortical bone, or compact bone, has a relatively homogeneous, compact and well-defined structure. Cortical bone substitutes have been made using epoxy, polymers and polymer composites, with acoustic properties falling within the wide range of reported values for cortical bone (Table 1). Liquid epoxy resins and hardeners have been mixed to create cortical bone materials, with one group reporting a speed of sound of 3168 m/s and attenuation of 3.7 dB/cm at 1 MHz, and another reporting 2740 m/s and 3.8 dB/cm at 1 MHz (Clarke et al. 1994; Tatarinov 1998). Pores were modeled for ultrasound porosity studies by introducing 0.8–1.5–mm–wide cubic particles of rubber in epoxy (Clarke et al. 1994; Hodgskinson et al. 1996; Tatarinov et al. 2005) (Fig. 3). The mineral content in bone was modeled by burning and grinding natural bone and subsequently mixing the mineral residue powder into epoxy (Tatarinov 1998).

One group exploring the use of polymers and polymer composites for use as cortical bone substitutes studied various materials within the desired speed of sound range, including ebonite (2200 m/s), acrylic (2500 m/s), carbon fiber plastics (4400 m/s) and fiberglass (no value reported) (Fig. 3) (Clarke et al. 1994; Hodgskinson et al. 1996; Tatarinov et al. 2005). Perspex, a type of acrylic glass, was reported to have a speed of sound of 2657 m/s, attenuation of 5.3 dB/cm MHz and density of 1180 kg/m^3 (Clarke et al. 1994; Hodgskinson et al. 1996; Tatarinov et al. 2005). Epoxies and rigid polymers and polymer composites can sufficiently approximate the acoustic properties of bone. However, rigid polymers and polymer composites are simpler models, whereas epoxy-based materials can be more closely tailored to the desired properties and configurations.

Trabecular bone

Trabecular bone, residing within cortical bone, has a porous structure that supports vascular tissues and contains marrow. Trabecular bone is difficult to model because of its tortuous framework and heterogeneity. In most cases, trabecular bone phantoms have been designed to contain bone marrow, and therefore the acoustic properties were tailored to more closely mimic marrow than trabecular bone itself.

Table 3. Acoustic properties of hard tissue substitutes

Material	Tissue	Velocity (m/s)	Attenuation (dB/cm)	Impedence (MRayl)	Source
Acrylic	Cortical Bone	2500	–	–	Tatarinov 1998
Carbon Fiber Plastics	Cortical Bone	4400	–	–	Tatarinov 1998
Ebonite	Cortical Bone	2200	–	–	Tatarinov 1998
Epoxy	Cortical Bone	2740–3168	3.7–3.8 @ 1 MHz	8.4	Clarke et al. 1994; Tatarinov 1998
Perspex	Cortical Bone	2657	5.3 @ 1 MHz	3.1	Clarke et al. 1994
Epoxy	Trabecular Bone	1844–3118	7–17 @ 0.5 MHz	–	Clarke et al. 1994
Polyvinyl Chloride	Whole Bone	2300	–	–	Barkmann et al. 2000
Dental Composite	Dentin	3306	108 @ 19 MHz	6.9	Singh et al. 2008
Aluminum	Enamel	6300	–	17.0	Blodgett 2003
Soda Lime Glass	Enamel	5789	6 @ 19 MHz	13.0	Singh et al. 2008

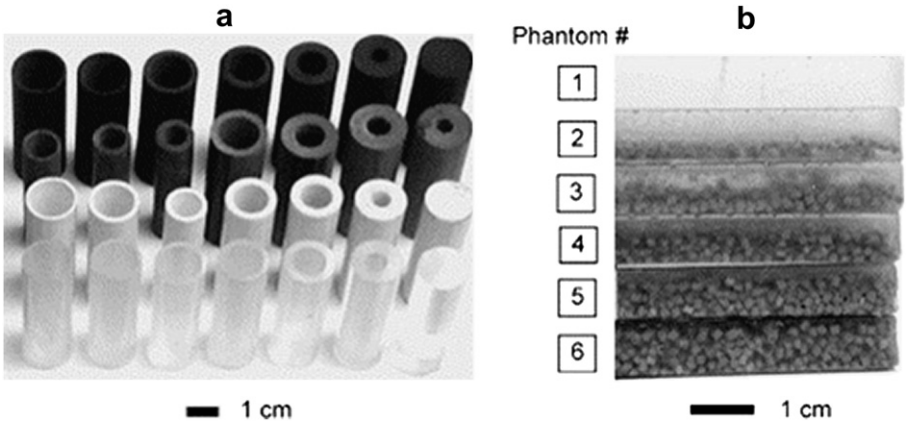

Fig. 3. Tubular specimens of ebonite, acrylic plastic, fiberglass and carbon fiber plastic (*left*) and layered cortical bone substitutes with rubber particles mixed in epoxy (*right*) (Tatarinov et al. 2005).

One group developed a trabecular bone substitute by adding 1 mm cubic gelatin granules to liquid epoxy, degassing and subsequently hardening the mixture (Clarke et al. 1994). A range of porosities was achieved by varying the volume of epoxy and gelatin, resulting in a speed of sound range between 1844 and 3118 m/s and attenuation between 7 and 17 dB/cm at 0.5 MHz (Clarke et al. 1994). A gelatin and water mixture was used as the marrow mimic. In another study, sunflower oil was embedded into the pores of the material to act as a marrow substitute (Strelitzki and Truscott 1998).

Trabecular bone phantoms have also been manufactured by introducing holes into Perspex acrylic resins and polyacetal materials, with the holes in the polyacetal filled with water to mimic marrow (Hodgskinson et al. 1996; Lee and Choi 2007). A phantom consisting of parallel nylon wires, simulating trabeculae, was built in 2-D rectangular grid arrays, with the thickness of nylon wires chosen to match the trabecular thickness (Wear 2005). Nylon wires were previously shown to exhibit frequency-dependent scattering similar to that exhibited by trabecular bone (Wear 2004).

Whole bone

Whole-bone phantoms include both cortical and trabecular bone substitutes. A phantom composed of glass beads dispersed in vulcanized silicone was used to assess a tool for measuring mineral density in women (Young et al. 1993). Polyvinyl chloride (PVC) tubes of varying diameters and a speed of sound of 2300 m/s were used as whole-bone phantoms in a study that used ultrasound to gauge fracture risk (Barkmann et al. 2000). Axisymmetric and nonaxisymmetric whole-bone phantoms were made to assess cortical bone thickness using ultrasound-guided waves, with axisymmetric phantoms built from acrylic tubes filled with water (Moilanen et al. 2007) and nonaxisymmetric phantoms made of PVC and filled with butter (Moilanen et al. 2004, 2007). A fetal skull bone phantom was built to validate the use of pulsed Doppler ultrasound in studying cerebral vasculature and was made from a high-density polyethylene (Vella et al. 2003). The phantom was reported to closely mimic the fetal skull bone both acoustically and thermally (Pay et al. 1998).

Finally, trabecular material was created using the epoxy and sunflower oil technique, and a whole-bone phantom was created by encasing it in a hollow Perspex cylinder and degassing it in a vacuum chamber for studies of osteoporotic fracture risk (Strelitzki and Truscott 1998).

Dental hard tissues

Teeth are primarily composed of enamel, the dense fibrous ceramic composite on the outer tooth surface and dentin, the inner structural material of a tooth that is formed from a mineralized collagenous matrix. Enamel was simulated using aluminum and dentin was simulated using copper in a study that used laser-based ultrasound to examine dental structure (Blodgett 2003). Aluminum was found to closely match enamel in compressional (6300 m/s) and shear (3100 m/s) wave speed of sound, as well as acoustic impedance (17.0 MRayl), but copper was a poor substitute for dentin.

Another group explored various glasses, ceramics and metals as tissue substitutes for enamel. Soda lime glass was ultimately selected because of its low attenuation (6 dB/cm at 19 MHz) and comparable compressional speed of sound (5789 m/s) and acoustic impedance (13 MRayl) (Singh et al. 2008). Self-curing resin-based dental composite was selected as a dentin substitute in the study over dental cements, epoxies and plastics because of its moldability and its comparable acoustic properties (c = 3306 m/s, A = 108 dB/cm at 19 MHz, Z = 6.9 MRayl) to dentin. The group was able to prepare tooth phantoms by injecting the composite material into a mold, curing

it and attaching the resulting composite ''dentin'' block to a diced glass ''enamel'' slab with composite cement. Cracks were embedded into the composite block during curing, and dental restorations, including silver-mercury amalgam fillings and gold and porcelain crowns, were also integrated into the phantoms (Culjat et al. 2005; Singh et al. 2007). However, unlike teeth with complex internal microstructures, the phantoms were prepared from two monolithic sections.

DISCUSSION AND CONCLUSION

Many soft tissue-mimicking materials have been described that have a compressional speed of sound, density, attenuation and acoustic impedance within the measured range of soft tissues (Tables 1 and 2). The backscattering coefficient, nonlinearity parameter and shear wave speed of sound (in the case of hard tissue substitutes) have rarely been reported and therefore are not included in the tables. Agarose-based materials have been the most widely used and are very well characterized in the literature. They have the advantage that they are simple to prepare, can be tailored to vary their acoustic properties and are able to support a uniform distribution of scatterers. However, agarose-based tissue substitutes are limited in size (typically <5 cm in thickness) because they must have high surface-to-volume ratios to properly congeal. The longevity of agarose-based materials is highly dependent on handling and storage.

Polyvinyl alcohol–based materials have a more complex fabrication process, which requires multiple freeze-thaw cycles. Like agarose-based materials, PVA materials can be acoustically tailored and can also support a uniform distribution of scatterers. However, PVA materials have good longevity and structural rigidity, they can be shaped and they are therefore the most attractive choice among the soft tissue substitutes when longevity and stability are of interest. Of the remaining tissue substitutes described here, each is limited either by its acoustic properties, by its stability or by its structure. Open cell foam–based materials cannot readily be acoustically tailored, but are unique in that localized pathologies can easily be embedded within a phantom. Oil gel–based tissue substitutes may have promise but have not been sufficiently characterized. Most gelatin-based substitutes have been limited by low Young's modulus and longevity.

Soft tissue phantoms have been described that have incorporated many of the soft tissue-mimicking materials described before. The most common tissue-mimicking materials used in the fabrication of solid organ phantoms have been those based from agarose, gelatin and PVA, with a mixture of water and glycerin as the most common blood substitute. Processes using agar and PVA were developed that enabled multiple layers of soft tissues to be combined to mimic multiple structures (Madsen et al. 1982; Frayne et al. 1993; Reinertsen and Collins 2006). However, the bulk of soft tissue phantoms have had homogenous internal structures. Soft tissue phantom research efforts have focused mostly on vascular and breast tissues.

Hard tissue phantoms have been developed using epoxies, plastics and ceramics, and have recently begun to advance with the advent of new materials and fabrication techniques. However, limited research has been applied to the study of hard tissue substitutes to date, and therefore a sufficient range of acoustic properties has not yet been achieved. The majority of hard tissue substitutes are simple and have good longevity, but their acoustic properties cannot easily be tailored. Like soft tissue substitutes, most hard tissue substitutes are homogeneous, and therefore lack the fibrous microstructure and corresponding asymmetry present in hard tissues. Of the hard tissue-mimicking materials described to date, epoxies have the most promise. Epoxies can be molded into the desired shape, and multiple studies have demonstrated that epoxies can be combined with other materials to achieve a range of acoustic properties (Table 3) (Clarke et al. 1994; Tatarinov 1998).

Although numerous tissue phantoms are now available commercially, customized tissue substitutes continue to have a role, primarily in the medical ultrasound research community. Additional soft and hard tissue substitutes will continue to be developed by academic and industry research groups primarily because of the low cost and design flexibility afforded by customized tissue-mimicking materials.

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