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Diagnostic Ultrasound Safety Review for POCUS Practitioners

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Summary

Potential ultrasound-exposure safety issues are reviewed with guidance for prudent use of "point of care" ultrasound (POCUS). Safety assurance begins with the training of POCUS practitioners in the generation and interpretation of diagnostically valid and clinically relevant images. Sonographers themselves should minimize patient exposure in accordance with the as-low-as reasonably-achievable (ALARA) principle, particularly for the safety of eye, lung and fetus (SELF). ALARA-SELF entails the reduction of output indices or exposure duration, consistent with acquisition of diagnostically definitive images. Informed adoption of POCUS worldwide promises reduction of ionizing radiation risks, enhanced cost-effectiveness and prompt diagnoses for optimal patient care.

Key Words: Ultrasound Bioeffects, diagnostic ultrasound safety, point-of-care ultrasound, ALARA, Safety for Eye Lung and Fetus (SELF), Output Display Standard, Thermal Index, Mechanical Index, FDA Regulation.

Introduction

Diagnostic ultrasound has provided non-ionizing radiation imaging for patient care for more than 50 years. In the past, the typical hospital diagnostic ultrasound machines were large cumbersome carts needing expert sonographers for production of useful diagnostic images, similar to CT or MRI procedures. However, advances in design of ultrasound machines have reduced the size while technological advances have improved image quality. In a radical departure from past practices, diagnostic ultrasound can now be easily portable and even 'handheld' - carried to the patient and applied by physicians or other trained individuals for immediate assessment and diagnosis with real time discussion leading to enhanced patient service. This advance compares to the introduction and adoption of the iconic physician's stethoscope in the 19th century for auscultation, and provides physicians with versatile ultrasonic imaging of virtually any part of the body [1]. This development has created a new medical topic of "point-of-care ultrasound" (POCUS) [2]. The appearance of POCUS research publications in the medical literature (PubMed) is rapidly increasing, see Fig. 1, and testifies to its scientific validation and growing importance in medical practice.

The use of POCUS has revolutionized the ability of clinicians to diagnose patients at the bedside rapidly and accurately. There are virtually no specialties in the House of Medicine which do not employ ultrasonography, either for diagnostic purposes, procedural guidance, or both. Training programs in a variety of fields and specialties offer advanced training with this specific imaging modality, and increasingly, ultrasonography is incorporated into medical school curricula. Ultrasonography offers a radiation-free, portable, and cost-effective means of imaging

almost every part of the body.

POCUS Patient Examinations

The rapidly expanding use of portable ultrasound machines allows diagnostic ultrasound to be performed by the physician at the bedside [3-5]. The total usage is impossible to determine because POCUS is performed in so many settings, often without billing records and often routinely on a daily basis to follow patient progress [6-8].

Rather than the comprehensive sonographic examination that typically is performed in the Radiology/ObGyn/Cardiology suite, POCUS provides a rapid answer to a specific clinical question. The versatility of ultrasound is extensive; see Table 1 for a list of clinical conditions that potentially can be ascertained with ultrasonography. For example, appropriately trained Emergency Physicians can effectively use ultrasound to accurately diagnose patients who present to the Emergency Department, including those with complaints related to early pregnancy [9], possible pericardial effusion [10], abdominal aortic aneurysm [11], undifferentiated shortness of breath [12], vision loss with retinal detachment [13] and those patients who have been traumatically injured [14]. The ability to perform and interpret these ultrasound examinations allows clinicians to diagnose potentially life-threatening conditions in a timely manner. In addition to the use of ultrasound in advanced healthcare environments, POCUS can be particularly beneficial in resource-poor locations. This modality can significantly alter management in places where other types of imaging are not available [15,16]. As an increasing number of physicians graduate from medical schools with knowledge of how to incorporate ultrasonography into their clinical practice, it is expected that the use of this technology will

continue to grow in a wide variety of healthcare settings.

Similar to adult medicine, pediatrics exemplifies the broad scope of POCUS being used in several disciplines such as critical care, emergency medicine, anesthesia, surgical subspecialties, as well as outpatient and inpatient pediatrics. Furthermore, its use is being expanded to new environments such as urgent care. As the first imaging exam for many patients, POCUS is invaluable as it provides real-time data that can be integrated into medical decision-making. In addition, it has become an integral part of numerous procedures including central and peripheral vascular access, incision and drainage of soft tissue pathology, nerve blocks, lumbar punctures, and bladder catheterization, among others. Furthermore, POCUS can be used either once or in an ongoing manner to monitor patients, due to the lack of any accumulating dose-effect (in contrast to ionizing radiation).

Benefits of POCUS are appreciated and endorsed by various societies, including the World Federation of Ultrasound in Medicine and Biology [17], The American College of Emergency Medicine [18], the Society of Critical Care Medicine [19, 20] and the American Academy of Pediatrics [21], among others. However, the consideration of possible risk related to ultrasound exposure often is brief and lacking in rationale for safety guidance. Medical ultrasound originated as a means for tissue modification, and numerous applications of ultrasound for therapeutic purposes have been developed and are in extensive use [22]. Diagnostic ultrasound examinations must be configured carefully to avoid possible adverse consequences for the patient, through Food and Drug Administration (FDA) regulation and application of sonographer training.

The non-ionizing radiation safety framework created by the FDA for assuring the safe use of diagnostic ultrasound with guideline upper limits on acoustic output has proven its worth as a flexible and effective system [23]. There have been no established occurrences of patient injury by diagnostic ultrasound [24, 25]. However, diagnostic ultrasound cannot be considered to be perfectly safe due to uncertainties about exposure dosimetry and potential injurious bioeffects. The safety issues are similar to those for all diagnostic ultrasound, but POCUS presents a new arena for assuring the safe use of diagnostic ultrasound. The purpose of this document is to briefly review and discuss potential ultrasound exposure safety issues and to outline guidance for prudent use of POCUS. As this was a review of existing literature and did not require the use of animals or patient data, ethical approval and request for obtaining informed consent were not required.

Background of Diagnostic Ultrasound Safety Considerations

Thermal and nonthermal physical mechanisms are operative during ultrasound exposure [26, 27]. There is essentially no risk of genetic injury from ultrasound (which exists for ionizing radiation in X rays, Positron Emission Tomography and Computed Tomography imaging). No universal dose quantity exists for ultrasound (such as the Gray, an ionizing radiation absorption quantity). The diagnostic ultrasound probe emits pulses of ultrasound which propagate into the body. There is no exposure to the operator, nor to bystanders, because ultrasound does not transmit into or propagate well in air, and the exposure is only to the tissues interacting with the pulses. The risks of specific biological effects induced by physical mechanisms of tissue

perturbation can be characterized by a threshold exposure response to ultrasonic output and duration, with zero risk below a threshold but an increasing impact above the threshold [26].

Diagnostic ultrasound exposure and biological effect mechanisms

Figure 2 illustrates an ultrasound pulse and its acoustic parameters (measured in water). The waveform in Figure 2a displays the ultrasound pressure wave (for reference, atmospheric pressure is 0.1 MPa), which can be characterized by a peak rarefactional (negative) pressure amplitude and a mean frequency. The pulse carries momentum and has an intensity, calculated from the pulse waveform in units of W/cm^2 (Fig. 2b). Figure 2c and 2d illustrate the exposure at a focal point during B-mode imaging, as the scanning beam of ultrasound passes by the measurement point, for an interval of a few pulse repetition periods, and for two full image frames. Note that the ultrasound exposure is minimal most of the time at a given point (e. g. the location of the small hydrophone used for pressure-field measurement) for scanned beams, so that the overall temporal-average intensity is much lower than the pulse-average intensity. Directed fixed beam modes (M mode and pulsed Doppler mode) have much higher temporal-average intensities than imaging modes because the beam is not scanned. Ultrasonic energy is attenuated and absorbed in tissue depending upon the absorption coefficient of the tissue. The attenuation is moderate for tissues like liver, high for bone, and very high for lung, and typically increases in proportion to mean ultrasonic frequency. Absorption of ultrasound in tissue results in an exponential decrease in ultrasound intensity as a function of propagation distance, which limits the penetration of ultrasound into the body, and requires strong time-gain compensation to display images with depth uniformity. Even though the image appears uniform, the ultrasound

exposure is much less for distal portions of an image relative to the focal point.

An assumption of safety for diagnostic ultrasound devices was codified by the Medical Device Amendments of 1976 enacted by the U.S. Congress. This act allowed for a simplified clearance process from the United States Food and Drug Administration (FDA) of new devices that were substantially equivalent in safety and effectiveness to devices legally marketed for the same applications before May 28, 1976. This law led to development of protocols for measurement of diagnostic ultrasound outputs, to the setting of guideline upper limits on the output of diagnostic ultrasound devices, and eventually to creation of exposure indices. Ultrasound machines are typically cleared for marketing by satisfying 510(k) premarket notification requirements of the FDA, including recommended upper limits to exposure parameters [23].

The FDA identified the acoustic intensity of ultrasound as the key quantity for regulation, and adopted the spatial-peak temporal-average intensity, I_{SPTA} in mW cm^{-2} and the spatial-peak pulse-average intensity, I_{SPPA} in W cm^{-2}, for characterization. These quantities are calculated from measurements of the pulse pressure waveforms in water using a hydrophone (Fig. 2). Furthermore, these measured values are used to estimate the peak intensities in scanned tissue by adjusting for tissue attenuation of the ultrasound, a process called derating. An attenuation coefficient of 0.3 dB cm^{-1} MHz^{-1} was adopted for this purpose as a conservative estimate of attenuation (typical tissues have higher coefficients) for safety. Using these methods and examination of pre-1976 devices, a table of maximal parameters was established for regulatory purposes. The values of $I_{SPTA.3}$ and $I_{SPPA.3}$ are listed in Table 2 (Mechanical Index values are also

listed, see the section on "The real-time display of acoustic output", below). Diagnostic ultrasound devices can be cleared by the FDA using these values via what is known as the Track 1 method of obtaining marketing clearance. An important feature of this Track 1 clearance method is that different recommended limits were established for different diagnostic ultrasound uses, with relatively low values for fetal (obstetrical) and ophthalmic uses.

The real-time display of acoustic output

Track 1 was unsatisfactory in that devices approved using this method have no indication of the actual acoustical output and exposure (except that it should be less that the Track 1 limits). In addition, the different values of $I_{SPTA.3}$ and $I_{SPPA.3}$ for different uses were not based on bioeffects studies, because such information was not available. Rather, to assist in FDA's decisions regarding substantial equivalence in terms of safety, they represented the maximum known output levels in each category for devices on the market before 1976 [28]. Physicians can prescribe use of an approved medical device for any examination deemed medically necessary, and the extent to which the Track 1 limits have been followed in practice is uncertain. The ultrasound community, specifically the American Institute of Ultrasound in Medicine and the National Equipment Manufacturers Association, worked with the FDA to create a standard for displaying output indicators to the sonographer that had defined relationships to physical mechanisms for biological effects of ultrasound [29]. This Output Display Standard was used to create a Track 3 method for device approval (there is no Track 2 method). This science-based method revolutionized the real-time assessment of exposure with direct relevance to safety and mostly eliminated the arbitrary limits for uses of modern diagnostic ultrasound machines (Table

2), which can generally perform most of the different types of exams.

The absorption of ultrasonic energy in tissue leads to local tissue heating, thereby introducing a thermal mechanism with the potential for tissue injury. Thermal Indices (TI) were created to indicate the potential for heating during diagnostic ultrasound examinations. Heating is dependent on the tissue absorption coefficient, the temporal average intensity, and the duration of exposure at a particular point. As noted above, the relatively high I_{SPPA} is reduced by pulsing the ultrasound to I_{SPTA}, and heating is further reduced by scanning the ultrasound beam, and by the relative motion of the transducer and body. Heating is typically highest near the probe and at the beam focus. The values of the TI capture the relative risk of thermal damage mechanisms during the ultrasound exposure [30, 31]. Specifically, TI values translate the acoustic output of the ultrasound machine, quantified by the I_{SPTA}, into an estimate of maximum potential temperature rise in °C in the tissue for long dwell times (i. e. the potential worst case). Since the ultrasound absorption properties vary based on tissue type, three different TI conditions have been defined. These are the TIS (Thermal Index Soft Tissue) for soft tissue applications, the TIB (Thermal Index Bone) when bone is expected to be present in the imaging region of interest where the ultrasound waves are focused, and the TIC (Thermal Index Cranium) when cranial bone is at the surface near the ultrasound probe. As a gauge of bioeffect risk, TI values less than or equal to 0.7 can be considered inconsequential for any duration, while values of 6 or higher indicate a risk of tissue injury for 1 min or longer durations, and are discouraged by regulatory guidance.

There are also nonthermal mechanisms for effects of ultrasound on tissues. Acoustic

radiation force generated as ultrasonic energy is absorbed, or acoustic radiation pressure, generated when ultrasound reflects from a surface, can cause perturbation of tissue [32]. The physical perturbations can be biologically significant for high intensity focused ultrasound [33], but are small for diagnostic ultrasound with minimal expectation of harm. Radiation forces can lead to fluid flow, which can be evident in an ultrasound image and useful for distinguishing cysts from tumors [34]. Radiation forces can also cause local tissue displacement within the focal beam and are the basis for elastography imaging. For the diagnostic ultrasound mode of shear-wave elastography, radiation force impulses generate tissue displacement, which produces shear waves useful for mapping tissue elasticity [35].

Acoustic cavitation describes the interaction of an ultrasound field with existing gas bodies or microbubbles, and is another mechanism by which ultrasound can produce biological effects in tissue. Diagnostic ultrasound pressure amplitudes are sufficient (note that the peak negative pressure in Fig. 2a of about 2 MPa equals a negative stress of 20 times the magnitude of atmospheric pressure) to warrant consideration of the possible occurrence of ultrasonic inertial cavitation, which is associated with several biological effects. Inertial cavitation occurs when the ultrasound pulse interacts with a microscopic cavitation nucleus, such as a microbubble of gas. Above a peak rarefactional pressure amplitude threshold, the nucleus expands explosively to 2 or more times its initial diameter and then collapses under the inertia of the inrushing fluid. This phenomenon can kill nearby biological cells and damage blood vessels by mechanical processes, and furthermore cause damage by free radical generation due to temperatures exceeding 5,000 Kelvin at the collapse point. By calculating the inertial cavitation thresholds for

many different microbubble sizes and ultrasound frequencies [36], minimum thresholds (for optimal nucleation) were found to increase as the square-root of frequency. This finding guided the creation of the on-screen Mechanical Index, defined as the peak rarefactional pressure amplitude (derated for tissue attenuation) divided by the square-root of the frequency and adjusted to in situ exposure. From the theory, the lowest threshold for inertial cavitation associated with the optimal size of nuclei (or microbubble) occurs at an MI = 0.4. However, the guideline upper limit of output for diagnostic ultrasound devices was set at MI=1.9. Of note, this limit value was determined from measurements of the output of a 2.25 MHz pre-1976 diagnostic ultrasound probe, and not by investigation of bioeffects and specific safety considerations [28]. The MI=1.9 value thus tolerates a theoretical risk of cavitational bioeffects possible under optimal conditions of nucleation for MIs in the range 0.4-1.9.

Current FDA 510(k) guidance for the Output Display Standard (Track 3) methods is given in Table 2. Manufacturers can choose to use either the $I_{SPPA.3}$ value or the MI value as the upper limit (note that these limits are different, and, for example, the $I_{SPPA.3}$ can exceed 190 W cm^{-2} at MI=1.9 for ultrasonic frequencies greater than about 2.25 MHz). The two use categories are a global inclusion of most uses, and ophthalmic use. The difference in the two Tracks is noteworthy for obstetrical use: the I_{SPTA} limit was effectively increased from 94 to 720 mW cm^{-2}. The newer diagnostic ultrasound modes of elastography and contrast-agent enhanced diagnostic ultrasound were not noted specifically in the regulatory recommendations. However, elastography complies with the Track 3 methods: the radiation force impulses are relatively long, but have MI <1.9 and have $I_{SPTA.3}$ < 720 mW cm^{-2} by virtue of relatively low pulse repetition

frequencies (e. g. 1 Hz or less). The modes used for contrast-agent enhanced diagnostic ultrasound fall under the recommendations in Table 2, and it is the microbubble-based agents which receive separate FDA approval as injectable drugs (with recommended ultrasound parameter limits noted in the package inserts). All ultrasound machines that display the safety indices have an explanatory document "Medical Ultrasound Safety" [37] included in the operator's instructions or other documentation as required by FDA regulations. The vendors of diagnostic ultrasound equipment should help to supply safety information and to facilitate the prudent use of ultrasound exposure whenever possible.

ALARA

The dosimetry and thresholds for biological effects of diagnostic ultrasound are not definitively understood and therefore uncertainty exists as to the possible risks of harm. Research on patient risks has been limited, and in fact, it is impossible to prove the absence of risk. Risk may depend on individual patient physiology in addition to physical exposure parameters. To prudently accommodate these uncertainties, authoritative bodies assessing the diagnostic ultrasound safety problem have recommended the implementation of the As Low As Reasonably Achievable (ALARA) principle [26, 38, 39]. The operator is responsible for implementing ALARA during ultrasound examinations. That is, the exposure duration and the acoustical output should be kept as low as is reasonably achievable, consistent with collection of diagnostically acceptable images. The exposure indices were developed for display on diagnostic ultrasound machines to inform sonographers of exposure outputs related to thermal and mechanical (nonthermal) mechanisms, described above. As a benchmark low-risk condition,

diagnostic output (excluding ophthalmology) with MI < 0.4 [40, 41] and TI < 0.7 [42, 43] are considered to be of negligible risk of ultrasound-induced biological effects for any exam duration. Simple instructions for implementing ALARA are [38]: "Select the right transducer, start with a low output level, and obtain the best image possible by using focusing, receiver gain, and other imaging controls. If that is not adequate for diagnostic purposes, then increase the output level. We can further implement ALARA by reducing the total ultrasonic exposure time." Diagnostic ultrasound may be used without reservation in most examinations for medical indications or for appropriate POCUS practitioner training [44-46]. However, ALARA should include the elimination of diagnostic ultrasound exposure with no medical purpose or benefit.

Safety Considerations for Specific POCUS Examinations

The possible risk varies greatly for different imaging modes, examination regions in the body, patient habitus and health status. A reasonable application of ALARA to diagnostic ultrasound should include adjustment of exposure Index values or duration for the exam at hand by knowledgeable sonographers. The following considerations of various types of POCUS examinations help to guide the safe use of diagnostic ultrasound.

Imaging involving low absorption tissue without gaseous nuclei

Many POCUS examinations are performed in adult tissues with low absorption giving TIS<2, and no bodies of gas [47], see Table 1. Liver and kidney are commonly examined for abnormal masses and blood flow. The heart is examined by echocardiography for assessment of function. Small parts imaging provides excellent images that can be presented at magnified image scales, and typically do not include bone or bodies of gas. Focused Assessment with

Sonography in Trauma (FAST) examinations can detect blood in the abdomen and pericardium (for lung, see pulmonary POCUS below). Diagnostic interventional ultrasound for guided vascular access or fine needle aspiration are excellent for reduction of potential patient injury through control of the penetrating needle. Tissues in the body wall, including intercostal spaces and abdominal wall, likewise have no bone or gas bodies in the imaging path.

Critically, the body does not appear to contain optimum cavitation nuclei for diagnostic ultrasound, likely due to the complete wetting and sterilization processes active in living tissue. Research on the occurrence of inertial cavitation in response to diagnostic ultrasound imaging of normal tissue has been negative, indicating that inertial cavitation-induced injury is non-existent or very rare for diagnostic ultrasound without the presence of microbubble contrast agents. Therefore, the Mechanical Index should be considered to be a general nonthermal exposure index, rather than a specific cavitation index (except for contrast enhanced diagnostic ultrasound, discussed below).

These examinations also typically use imaging with low TI values (low temporal-average intensity) even at the maximum output. Heating is least for the low absorption soft tissues (i. e. other than bone or cranium) and presents minimal risk of injury, particularly in adults, for TI<2 even for lengthy exposure times, as listed in Table 3. Therefore, the risk of injury from the thermal mechanism is also very low.

For low absorption tissue without gaseous nuclei, the maximum output can be used with very low risk of patient injury from the ultrasound exposure. The ALARA principle should still be applied when reduced output imaging produces diagnostically optimal images in order to

avoid higher exposures with no additional medical value.

Contrast Enhanced POCUS

The use of ultrasound contrast agents to improve suboptimal ultrasound images and provide additional diagnostic information can be useful in several different situations such as echocardiography and assessment of liver masses [48, 49]. Contrast enhanced diagnostic ultrasound requires venous access for contrast agent injection along with coordinated timing of injection and imaging. Contrast agents are suspensions of stabilized microbubbles, which are designed for long circulation times and strong echo response.

Contrast enhanced diagnostic ultrasound has a known potential risk factor due to cavitation nucleation from the stabilized microbubbles [50]. This risk can be mitigated by use of low MI imaging modes (MI<0.4) designed for microbubble persistence and optimal contrast enhancement. However, there are also non-ultrasound related risks, although rare, such as injection site complications, Complement Activation Related Pseudo-Allergy (CARPA), and other anaphylactoid and allergic reactions [40, 49].

Use of contrast enhanced ultrasound is beginning to expand into the point of care setting focusing on cardiac and trauma related indications [51, 52]. However, given the complex interaction of contrast agent, examination protocol and system settings that can alter the cavitation risk, detailed safety parameters are beyond the setting of this review. In general, for imaging with contrast agents at an MI above 0.4, practitioners should use the minimal agent dose, MI, and examination time consistent with efficacious acquisition of diagnostic information.

Head, musculoskeletal examinations with bone and high TI modes

Musculoskeletal POCUS can be valuable for numerous diagnoses of head and musculoskeletal examinations (Table 1). A classic example of an important diagnosis perfectly suited to POCUS is examination for rib fractures. Griffith et al [53] found that rib sonography was better at detecting rib fractures than chest radiography. Additional uses include assessment for skull fracture, neonatal interventricular hemorrhage, transcranial Doppler, fluid in sinuses, etc.

These examinations are not expected to involve cavitation risk. However, bone and tendon have high absorption coefficients and will heat faster and to higher temperatures than soft tissue. The TI for bone (TIB) should be used for guidance when examinations involve bone and the TI for the cranium (TIC) should be used for examination of the head. For high TI (>0.7) conditions, the exposure time should be limited during an examination. A multi-step system is shown in Fig. 3 and Table 3 [43, 54]. In febrile patients, the temperature elevation should be added to the on-screen TI to determine the exposure time. The exposure time limit decreases exponentially with increasing TI (the horizontal scale in Fig. 3 is logarithmic). Sonographers encountering the higher TI values may advantageously reduce the TI (power output) to avoid hurried performance of difficult exams. For a TI of 5, a 50% reduction in power (-3 dB, equivalent to an MI reduction, for example, from 1.4 to 1.0) cuts the TI in half, thereby allowing an exposure time of 1 h rather than 1 min.

Ophthalmic POCUS

Ocular ultrasound is used at the bedside to diagnose many ophthalmic conditions, including intraocular or periorbital foreign bodies, globe rupture, hyphema, lens dislocation, lens

subluxation, retinal detachment, retinal hemorrhage, vitreous detachment, vitreous hemorrhage, choroidal detachment, papilledema, increased intracranial pressure, neoplasms, and vascular pathologies [55, 56]. The examination typically is conducted with a 7-15 MHz, small-footprint linear probe coupled to the closed eyelid with a copious amount of gel to permit successful visualization without excessive pressure to the globe. If the ultrasound device lacks an "ophthalmic" preset, then frequently a "small parts" preset is chosen. B-mode imaging is used for identifying anatomical abnormalities and the presence and location of foreign bodies, while Doppler ultrasound, both color and spectral, finds use in examining blood flow in the ophthalmic and central retinal arteries and veins [55].

The possibility of both thermal and nonthermal bioeffects should be considered in the eye. In a review by van Rhoon et al. [57], safe thresholds for temperature rise in various tissues and organs, including the eye, were expressed in terms of thermal dose of cumulative effective minutes at 43 °C (CEM43). The most sensitive eye structures were the lens, cornea, and retina, with the lowest CEM43 value being 2.4 minutes for the lens. One could base temperature-exposure time thresholds on this value, or alternatively, take a more conservative thermal dose-based approach by using the AIUM [41] "Statement on Mammalian Biological Effects of Ultrasound In Vivo" for fetal exposures to set a CEM43 of 0.125 minutes for the eye. The eye and early first-trimester embryo have some comparable characteristics in that they can have similar size, neither is well-perfused, and protein is present [58]. However, a practical problem with either of these thermal dose approaches is that users only have access to the TI, not the actual temperature rise, and studies have found that the TIS could greatly underestimate the

actual temperature rise in the eye [59,60]. The likely reason is that the generic tissue models used for the TIS are not appropriate for the eye, chiefly due to the relatively large absorption in the lens and orbital fat; also, the eye is poorly perfused. To offer some guidance, the British Medical Ultrasound Society has recommended not to exceed a TI of 1 when scanning the eye [61].

Regarding nonthermal bioeffects, the eye normally has no gas body content. However, there are some clinical situations such as trauma, surgery, or after the use of perfluorocarbon gases for treatment of retinal detachment in which gas bodies might be present [62]. In these cases, the risk of cavitational nonthermal effects is possible.

Development of TI and MI recommendations for eye exams is challenging because the aforementioned generic tissue models used for calculating these indices are not applicable for the eye. For this reason, the FDA diagnostic ultrasound guidance [23] has lower recommended maximum exposure levels for ophthalmic exams of $I_{SPTA.3} \leq 50$ mW cm^{-2}, MI ≤ 0.23, and TI ≤ 1 for devices that follow the Output Display Standard (Table 2). Temperature rise measurements in the eye due to ultrasound exposure have been described in several papers, which indicate that the risk of thermal injury is mitigated by the FDA guidelines for ophthalmic exams [60, 62, 63]. Silverman et al. [62] studied the safety of very high frequency diagnostic ultrasound (ultrasonic biomicroscopy) at 38 MHz and found no injury in histology for up to 30 min exposure of rabbit cornea or lens with $I_{SPTA.3} = 34$ mW/cm^2 (i. e. less than the FDA recommended limit of 50 mW/cm^2). In general, the eye should only be evaluated if there is an ophthalmologic preset on the system. If ophthalmologic setting is not available, the patient should be informed that the scan is an off-label use and give appropriate informed consent.

Pulmonary POCUS

The first accepted use of pulmonary diagnostic ultrasound was to rule out pneumothorax [64]. Subsequently, diagnostic ultrasound has been found to be valuable in the diagnosis of pneumonia, pulmonary edema, pulmonary embolism, atelectasis, diffuse parenchymal disease, respiratory distress syndrome, and lung cancer [65]. The pleura appears in the image as a hyperechoic line. Artifacts are used to facilitate a variety of diagnoses, including B lines (comet-tail artifacts), which are diagnostic for pulmonary edema or interstitial lung disease [66]. Chest sonography is used in children for the diagnosis of neonatal respiratory distress syndrome [67], pneumonia [68-70], and other neonatal pulmonary diseases using POCUS [71]. The assessments of B-lines and other image features are valuable in neonatal examinations for diagnosis of respiratory distress syndrome [72], assessing surfactant treatment [73], pulmonary hemorrhage [74] and the number of B lines correlates with computed tomography findings [75]. The total usage of pulmonary diagnostic ultrasound is impossible to determine because POCUS is performed in so many settings, and often routinely on a daily basis to follow patient progress.

The biological effect of pulmonary capillary hemorrhage (PCH) produced by pulsed ultrasound exposure relevant to diagnostic imaging was discovered more than 25 y ago in mice, [76] and has been confirmed in mice, rats, rabbits, pigs and monkeys. Direct human bioeffects research ethically cannot be done, although an early clinical study (B lines were not yet established as a lung ultrasound finding) was conducted to check for PCH on lungs of adult humans undergoing transesophageal echocardiography with exposure of the lung and thoracotomy, allowing lung examination [85]. No hemorrhage was noted by the surgeon on

gross examination of the lungs. Recent results on the induction of pulmonary capillary hemorrhage from diagnostic ultrasound imaging in rats was comparable to early results with laboratory pulsed ultrasound, and the ultrasound images displayed B lines associated with the occurrence and progression of this bioeffect [77, 78]. Animal research has shown that the PCH bioeffect depends on physical parameters, such as the ultrasound mode [79] and duration [80], in addition to the MI. Biological factors also are very important, including sedation [81], ventilation [82], age and lung position [83] and animal species [84].

The physical mechanism for the PCH bioeffect is uncertain, because both the thermal mechanism and cavitation have been ruled out, and a nonthermal mechanism such as acoustical radiation force or pressure may be important [86]. The most recent consensus report of the American Institute of Ultrasound in Medicine [87] states that, although it was clear that pulmonary capillary hemorrhage might occur during realistic diagnostic exposures above an MI of 0.4, patient risk should be minimal for diagnostic ultrasound, because only incidental lung exposure was expected. However, as noted above, pulmonary diagnostic ultrasound is now routine and widely performed using portable point-of-care machines. Clear application of the ALARA principle is needed.

Unfortunately, the B line sign of pulmonary capillary hemorrhage induction is not useful for safety guidance. The possibility of PCH induction for pulmonary examinations for MI>0.4 likely can be excluded when no B lines are seen, although very small PCH can escape detection [80]. However, the possibility of ultrasonic PCH induction for pulmonary examinations with MI>0.4 cannot be excluded when B lines are seen, due to ambiguity in the origin and persistence

of the B lines. B line artifacts being sought for diagnostic indications and those being induced by the diagnostic ultrasound itself would be impossible to clearly distinguish, particularly in clinical exams, due to large variation in B line appearance with lung sliding and hand motion of the probe.

The prudent safety guidance for pulmonary ultrasound is to practice ALARA with an MI<0.4 in many patients. Because the lung surface is often at shallow depth, 0.7 cm even in some adults [88], pulmonary images may be obtained at a reduced MI. An additional safety margin exists for many pulmonary exams, such as in high BMI patients, because the intercostal tissue has a relatively high absorption coefficient of about 1.2 dB cm^{-1} MHz^{-1} (which is higher than the value (0.3) assumed for the MI). The actual exposure at the pleura will be less than that indicated by the on-screen MI. For a chest wall thickness of 4 cm and an ultrasound frequency of 6 MHz, not an uncommon configuration, the exposure implied by the on-screen MI could be less by a factor of 10 at the visceral pleura, mitigating the risk of lung injury for MI>0.4. These considerations should be factored in to the patient-specific application of the ALARA principle, consistent with acquisition of diagnostically acceptable images.

Obstetrical POCUS

Ultrasound is the imaging modality of choice for obstetrics- and gynecology-related emergencies as it can be used to rapidly identify the uterus and its contents. In addition, the adnexa can be evaluated and the pelvis can be assessed for the presence of free fluid. Trans-abdominal ultrasound (TAU) scanning will be the first approach but trans-vaginal ultrasound (TVU) will often be needed for its superior resolution. Common causes of acute lower

abdominal pain in females include ovulation pain, ovarian torsion, hemorrhagic cysts, endometriosis, pelvic inflammatory disease, ectopic pregnancy, issues with an intra-uterine contraceptive device, degenerating fibroids, as well as non-gynecologic causes such as appendicitis. In obstetrics, POCUS can be used as a straightforward and accurate method to visualize an intra-uterine pregnancy from 5-6 weeks gestation to term. One of the most common indications for POCUS is abdominal pain in a patient with a positive pregnancy test. Besides location of the pregnancy, ultrasound can be used to confirm viability (presence of a fetal heartbeat), fetal number, gestational age and, later in pregnancy, to assess fetal presentation, growth and wellbeing as well as placental location, cervical length and quantity of amniotic fluid [89]. Ultrasound is also used for prenatal imaging of fetal ocular and orbital abnormalities [90].

While there are no concerns with the use of ultrasound in gynecology, whenever there is the possibility of an intrauterine pregnancy, caution should be exercised [58]. The developing fetus is mostly susceptible to external insults in the first 10-12 weeks of pregnancy, the time of embryogenesis/organogenesis. The use of prenatal ultrasound for inspection of the eyes also introduces the safety considerations for the eye, noted above in the Ophthalmic POCUS section. Importantly, a 20 year follow up study of a randomized controlled trial found that no significant impact on visual outcomes or ocular biometry was associated with frequent in-utero ultrasound (B mode and spectral Doppler mode, likely including ocular exposure) [91]. The occurrence of cavitational bioeffects or pulmonary capillary injury in the fetus is unlikely due to an absence of cavitation nuclei and the lack of gas in the fetal lungs and bowels. However, heat is a known teratological agent, from animal research as well as from the described incidence of fetal

anomalies in human mothers with elevated temperature from infection early in pregnancy or secondary to an excessive use of hot baths or saunas. Therefore precaution is necessary, particularly in modes that can generate higher acoustic outputs, such as spectral (pulsed) Doppler mode. This has led to joint statement recommending against the routine use of pulsed Doppler in the first trimester [39]. In keeping with the ALARA principle this would advocate for using M mode and not using pulsed Doppler for the measurement of fetal heart rate alone.

The general recommendation should be to keep the examination as short as possible, with as low as possible acoustic outputs but sufficient to arrive at the correct diagnosis (ALARA principle). The thermal index TIS should be used prior to 10 weeks and the TIB after 10 weeks. Detailed advice on the maximum scanning time for a given TI is listed in Table 3. As for the adult case, a reduction in output can greatly lengthen the recommended scanning time limit. For example, a reduction in output power of 50% for a TI of ~3 reduces the TI to ~1.5, thereby allowing an exposure time of up to 30 min rather than <1 min.

Discussion of Ultrasound Safety in the POCUS Perspective

Reduction in Ionizing Radiation Dose

This review has focused on safety considerations for non-ionizing ultrasound exposure. However, it should be noted that POCUS has no risk of bioeffects such as cancer, and no trend for increasing risk with exposure accumulation, as are well known for ionizing radiation doses. This feature of ultrasound examination provides an overall benefit by reducing ionizing radiation dose. POCUS is growing throughout all medical specialties, including Pediatrics. Historically,

ultrasound in pediatrics was used in traditional ways by both Radiology and Cardiology. The goal of bedside ultrasound, aka POCUS, is to provide real-time information to clinicians at the point-of-care to guide medical decision-making and provide procedural guidance. It is well established that radiation exposure in children has long-term effects [92-96]. Use of ultrasound can reduce the ionizing radiation exposure substantially. For example, POCUS has proven of value for monitoring Crohn's disease in children [97] and can greatly reduce the cumulative ionizing radiation dose over the long course of this disease [98].

Hands on training for high quality POCUS

The most important factor for POCUS efficacy and safety is operator training. Physicians and other medical personnel who may use POCUS must understand the principles of ultrasound imaging, the use of the exposure indices, and how to produce images of diagnostic value. Missed or incorrect diagnoses can have substantial adverse consequences for the patient. Numerous training guides are available, for example, in surgery residency [99], anesthesiology [100], pediatrics [101], emergency medicine [18], resource limited emergency physicians [102], critical care [19] and clinical practice [103]. Hands-on training is critical, and represents an important medical application of diagnostic ultrasound (with attention for potential incidental findings of medical importance) [45, 46]. Ultrasound imaging has become more and more clear and accurate, but will show nothing of value in the wrong hands. A particularly exciting aspect of POCUS is that appropriate training including safety and image interpretation potentially can be given to many non-physician medical personnel and bring the benefits of POCUS to virtually any patient in need; for example, in remote rural areas [104, 105].

Summary of POCUS Safety Guidance

Diagnostic ultrasound exposure is regulated for safety and may be used without reservation in most examinations for medical indications or for appropriate POCUS practitioner training. Non-medical uses should be minimized or avoided [44]. No diagnostic-ultrasound induced adverse biological effects have been demonstrated and confirmed in humans, but very little definitive human experimentation has been performed (due to problematical ethics and low sensitivity). Based on theoretical considerations and definitive animal studies, special attention and prudent use of the ALARA principle should be considered in three situations. The eye is particularly vulnerable and has special, separate FDA guidelines (Table 2), which must be set by the user for most ultrasound machines. The surface of the lung is excellent for diagnostic examination but may have a risk of capillary hemorrhage in some patients who are thin or treated by some medications. The fetus, as always, must prudently be considered to be vulnerable and examined with care by using the correct TI value for exposure limitation. Sonographers themselves must practice ALARA patient exposure during POCUS. Remembering these special situations may be aided by the acronym: Safety for Eye Lung and Fetus (SELF).

POCUS represents a revolution in patient care with timely and high value diagnostic information. It is cost effective and can fill the need for medical imaging in many venues including the most remote settings. With few areas of concern for ultrasound exposure, the use of POCUS can reduce patient exposure to ionizing radiation, which is an overall benefit for patient safety. Continued growth and acceptance of POCUS will provide optimum patient care.

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Table 1. A list of clinical conditions which can be potentially ascertained with ultrasonography at the bedside.

Head:
- Skull fracture
- Neonatal interventricular hemorrhage
- Transcranial Doppler

Ocular:
- Retinal detachment
- Vitreous hemorrhage
- Dilated optic nerve sheath (as manifestation of elevated intracranial pressure)
- Globe rupture
- Retrobulbar hemorrhage

Face:
- Fluid in sinuses
- Peritonsillar abscess

Neck:
- Lymphadenopathy vs abscess
- Thyroid masses
- Orotracheal airway evaluation

Cardiac:
- Cardiac activity in setting of cardiac arrest
- Pericardial effusion
- Cardiac tamponade
- Estimation of left ventricular ejection fraction
- Focal wall motion abnormality
- Preload and response to therapy
- Evaluation of right ventricular function

Lung:
- Pleural effusion
- Thoracentesis
- Interstitial alveolar syndrome
- Pulmonary edema
- Pneumothorax
- Acute heart failure

Pneumonia
ARDS (Acute Respiratory Distress Syndrome)

Abdomen:
Biliary disease
Hemoperitoneum
Small Bowel Obstruction
Hernia
Appendicitis
Pyloric Stenosis
Intussusception

Pelvic:
Intrauterine pregnancy
Ectopic pregnancy
Ovarian masses
Ovarian torsion
Pelvic inflammatory disease

Genitourinary:
Hydronephrosis
Testicular torsion
Bladder volume (urinary retention)

Procedural:
Lumbar Puncture
Central Venous Catheterization
Peripheral vascular access
Regional anesthesia
Abscess localization
Paracentesis
Thoracentesis
Procedural complications

Musculoskeletal:
Fractures: Rib. Extremity, Skull
Tendon injuries

Vascular:
DVT
Superficial thrombophlebitis

Abdominal Aortic Aneurysm
Aortic Dissection
Arterial thrombosis
IVC (volume assessment)
Arterial access

Table 2. The values of recommended maximal output exposure levels for the two FDA 510k approval tracks, adapted from FDA [23]. For both Tracks, either the $I_{SPPA.3}$, or the MI limits may be used.

USE	$I_{SPTA.3}$(mW cm^{-2})	TI	$I_{SPPA.3}$(W cm^{-2})	MI
Pre-amendments Acoustic Output Exposure Levels (Track 1)				
Peripheral	720	-	190	1.9
Cardiac	430	-	190	1.9
Fetal & Other*	94	-	190	1.9
Ophthalmic	17	-	28	0.23
Output Display Standard Recommendations (Track 3)				
Global Maximum	720		190	1.9
Ophthalmic	50	1.0	-	0.23

* Abdominal, Intraoperative, Pediatric, Small Organ (breast, thyroid, testes, etc.), Neonatal Cephalic, Adult Cephalic
$I_{SPTA.3}$ = Derated Spatial-Peak Temporal-Average Intensity
$I_{SPPA.3}$ = Derated Spatial-Peak Pulse-Average Intensity
TI = Thermal Index
MI = Mechanical Index

Table 3. Recommended limitations on exposure time for high TI settings of the appropriate TIS, TIB or TIC.

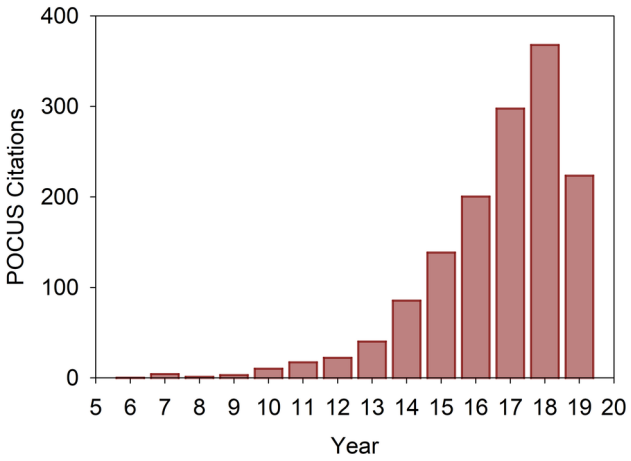
Thermal Index Range	Adult Scanning Time	Obstetric Scanning Time
°C	minutes	minutes
> 6	Not Recommended	Not Recommended
5.0 – 6.0	< 0.25	Not Recommended
4.0 – 5.0	< 1	Not Recommended
3.0 – 4.0	< 4	Not Recommended
2.5 – 3.0	< 15	< 1
2.0 – 2.5	< 60	< 4
1.5 – 2.0	< 120	< 15
1.0 – 1.5	No Time Limit	< 30
0.7 – 1.0	No Time Limit	< 60
< 0.7	No Time Limit	No Time Limit

Figure Captions.

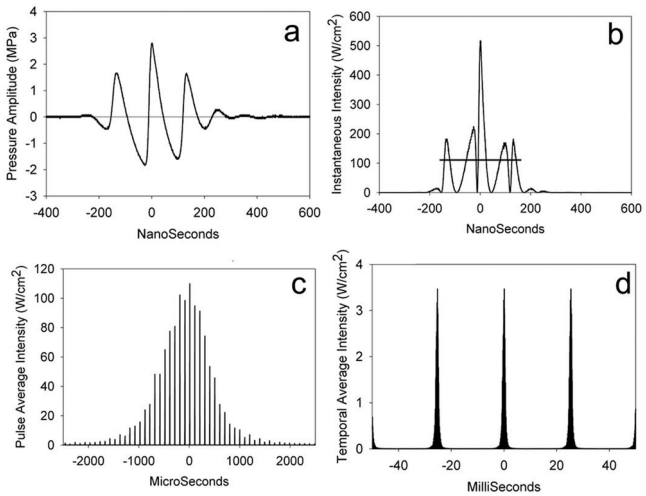
Figure 1. A plot of the number of citations returned in a PubMed search for "point-of-care ultrasound" for each the last 15 years (* up to June 2019). The rapid development of a POCUS research literature testifies to its growing importance in medical practice.

Figure 2. Measured signals from a hydrophone in the scan plane of a 7.6 MHz diagnostic ultrasound probe operated at an on-screen MI of 0.9 reduced (derated) to approximate the ultrasound values reaching a rat lung surface. The pulse wave form (a) is shown as pressure versus time, which is used to calculate the instantaneous and pulse average (horizontal line) intensities (b). In (b), the length of the line indicates the pulse duration of 320 ns. As the beam passes by the probe, a series of pulses was received (c), which related to the scan rate and the width of the beam. The pulse repetition frequency in (c) was 10 kHz (100 μs repetition period). The imaging was continuous at 39 frames-per- second, which is seen as a brief series of pulses, as in (c), repeated each 25.6 ms (d).

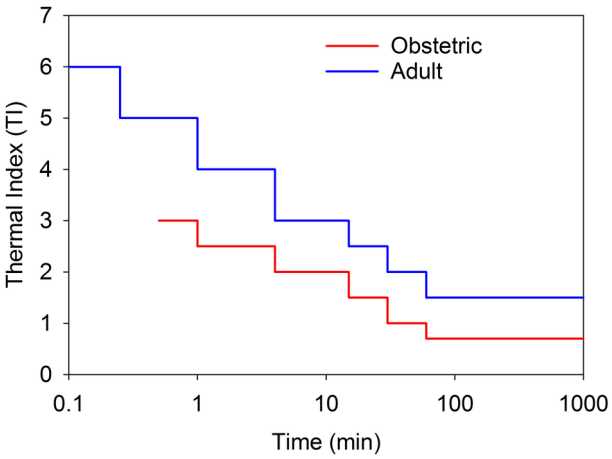
Figure 3. Recommended TI versus exposure time safety guidance for the appropriate TIS, TIB or TIC (Table 2). Note that on the logarithmic time scale, small changes in TI result in large changes in the recommended time limit.



JUM_15202_Figure 1.tif



JUM_15202_Figure 2.tif



JUM_15202_Figure 3.tif

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The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
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Royalties: Funds are coming in to you or your institution due to your patent

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1. Given Name (First Name): Eitan
2. Surname (Last Name): Dickman
3. Date: 30-September-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Douglas Miller

5. Manuscript Title: Diagnostic Ultrasound Safety Review for POCUS Practitioners

6. Manuscript Identifying Number (if you know it): JUM-2019-06-0599.R1

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Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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Dr. Dickman has nothing to disclose.

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