Current Ultrasound Technologies and Instrumentation in the Assessment and Monitoring of COVID-19 Positive Patients

Xuejun Qian, *Member, IEEE*, Robert Wodnicki, *Member, IEEE*, Haochen Kang, *Graduate Student Member, IEEE*, Junhang Zhang, Hisham Tchelepi, and Qifa Zhou, *Fellow, IEEE*

***Abstract*— Since the emergence of the COVID-19 pandemic in December of 2019, clinicians and scientists all over the world have faced overwhelming new challenges that not only threaten their own communities and countries but also the world at large. These challenges have been enormous and debilitating, as the infrastructure of many countries, including developing ones, had little or no resources to deal with the crisis. Even in developed countries, such as Italy, health systems have been so inundated by cases that health care facilities became oversaturated and could not accommodate the unexpected influx of patients to be tested. Initially, resources were focused on testing to identify those who were infected. When it became clear that the virus mainly attacks the lungs by causing parenchymal changes in the form of multifocal pneumonia of different levels of severity, imaging became paramount in the assessment of disease severity, progression, and even response to treatment. As a result, there was a need to establish protocols for imaging of the lungs in these patients. In North America, the focus was on chest X-ray and computed tomography (CT) as these are widely available and accessible at most health facilities. However, in Europe and China, this was not the case, and a cost-effective and relatively fast imaging modality was needed to scan a large number of sick patients promptly. Hence, ultrasound (US) found its way into the hands of Chinese and European physicians and has since become an important imaging modality in those locations. US is a highly versatile, portable, and inexpensive imaging modality that has application across a broad spectrum of conditions and, in this way, is ideally suited to assess the lungs of COVID-19 patients in the intensive care unit (ICU). This bedside test can be done with little to no movement of the patients from the unit that keeps them in their isolated rooms, thereby limiting further exposure to other health personnel. This article presents a basic introduction to COVID-19 and the use of the US for lung imaging. It further provides a high-level overview of the existing US technologies that are driving development in current and potential future US imaging systems for lung, with a specific emphasis on portable and 3-D systems.**

***Index Terms*— Comorbidity, computed tomography (CT), COVID-19, imaging, linear arrays point of care ultrasound (POCUS), ultrasound (US).**

I. Introduction

AT THE end of 2019, a new virus in the coronavirus family was identified as being responsible for a new wave of respiratory infections in Asia that later spread worldwide. This new virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after the original SARS outbreak of 2002–2004. On February 12, 2020, the World Health Organization (WHO) renamed the disease caused by SARS-CoV-2, Coronavirus Diseases 2019, or simply, COVID-19. Later in March 2020, with the rapid worldwide spread of COVID-19, positive case rates significantly higher than when initially identified, and with many more severe clinical manifestations than those of the seasonal influenza virus, WHO officially declared COVID-19 a pandemic and unprecedented healthcare crisis. Since it first emerged in Asia, the outbreak has now spread across the globe with a total number of reported cases worldwide reaching more than 10 000 000 as of this writing.

Since COVID-19 is highly contagious and may lead to acute respiratory distress or multiple organ failure in severe cases, a group of international experts, with a range of specializations, including clinical and scientific communities,

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Xuejun Qian and Qifa Zhou are with the Department of Biomedical Engineering, University of Southern California, Los Angeles, CA 90089 USA, also with the NIH Resource Center for Medical Ultrasonic Transducer Technology, University of Southern California, Los Angeles, CA 90089 USA, and also with the Keck School of Medicine, Roski Eye Institute, University of Southern California, Los Angeles, CA 90033 USA (e-mail: qifazhou@usc.edu).

Robert Wodnicki, Haochen Kang, and Junhang Zhang are with the Department of Biomedical Engineering, University of Southern California, Los Angeles, CA 90089 USA, and also with the NIH Resource Center for Medical Ultrasonic Transducer Technology, University of Southern California, Los Angeles, CA 90089 USA.

Hisham Tchelepi is with the Keck School of Medicine, University of Southern California, Los Angeles, CA 90033 USA (e-mail: hisham.tchelepi@med.usc.edu).

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has taken swift action to try to control the outbreak. With no specific disease treatment yet identified, early detection and isolation of infected individuals are critical for controlling disease spread in the community. An important tool for this detection is medical imaging, including magnetic resonance imaging (MRI), computed tomography (CT), chest X-ray (CXR), positron emission tomography (PET), and ultrasound (US), among others.

Both CXR and CT can reveal abnormalities indicative of lung disease, including COVID-19 [1], [2]. Compared with CXR, chest CT is superior for identifying early COVID-19 disease changes. According to recent reports in clinical studies [3], chest CT is highly sensitive for detecting certain characteristic findings in the lung associated with COVID-19, as well as for monitoring progression and staging of the disease. There is a significant debate currently on the role of CT as an adjunct to or replacement for nucleic acid testing, which is considered to be a gold standard for diagnosing COVID-19 in screening. In addition, it is recognized that CT, while providing high-quality images for the lung, may not be a practical tool in the COVID-19 pandemic due to the issue of cross-contamination with other patients and the associated requirement to clean the system after every COVID-19 imaging exam [4].

As the number of patients infected with COVID-19 continues to rise globally, both clinicians and researchers are seeking alternative imaging approaches for quick assessment of acute respiratory failure and pneumonia in these patients, especially in the intensive care unit (ICU). In contrast to CXR and CT, the US is viewed as cost-effective and highly portable, can be performed at the bedside [5], and is, therefore, a promising alternative to address these requirements. Significant clinical experience in the use of the US for lung exists [6]–[8], and recent work has shown that it is applicable to COVID-19 as well [9]–[12]. The diagnostic accuracy of lung US has been shown to be similar to chest CT scans in patients presenting with respiratory complaints, such as dyspnea and hypoxemia, caused by non-COVID-19 pneumonia [13], [14]. Normal lung US findings correlate well with chest CT scans showing the absence of typical ground-glass opacities. Poggiali *et al.* [12] affirmed that the US is a sensitive and specific alternative to chest CT for COVID-19.

Recent developments in the integration of electronics [15]–[17] and the use of highly sensitive and wideband materials (e.g., piezoelectric single crystals with fractional bandwidth $>$ 70%) [18], [19] have brought significant improvements to US equipment in general and highly portable point of care US (POCUS) in particular. Modern US units are ideally suited for use at the patient bedside, which is advantageous for use in the ICU for COVID-19. In addition, these new systems are already used for diagnosing conditions of the heart [20], [21] and the vasculature [22], [23], which also represents an important burden of comorbidity in the COVID-19 epidemic [24]. These highly portable devices interface directly to smartphone and tablet-based image display functions [25] for convenient use. There has also been some early work in the application of 3-D volumetric imaging to lung US [26]. These 3-D imaging systems rely heavily on integrated microelectronics [15], [17] that are critical for data acquisition for a large number of element channels present in a 2-D array. Finally, a wide selection of imaging frequencies can potentially improve image quality for lung [27], and novel transducer materials and device structures have been introduced in recent years [18], [19], which are potentially beneficial for this purpose.

Since significant effort has been made in recent years to improve the image quality and convenience of US devices from all of the abovementioned aspects, US now plays a more important role in clinical diagnosis, especially for point of care purposes. During the COVID-19 pandemic, such a versatile US technique immediately attracted great interest from both clinicians and researchers on the basis of its real-time and portable capability, resulting in the need to understand current US technologies and instrumentation in the assessment and monitoring of COVID-19 positive patients.

In this article, therefore, we aim to systematically review the role of US from the transducer level to the imaging system level with a specific emphasis on the role of these technologies for COVID-19. In Section II, we discuss the role of US technologies in COVID-19. In Section III, we review 1-D US array technology that is the main US instrument currently used for lung US. In Section IV, POCUS technology is highlighted. Section V presents the state of the art for electronics for volumetric imaging probes, with a view toward potential application in portable systems for lung imaging. Novel imaging techniques and transducer devices with potential applications for improved imaging in the lung are also presented.

II. Role of US in COVID-19

A number of excellent review articles exist in the medical literature for the use of US for diagnosis of acute lung injury [6]–[8]. In this section, we provide a brief summary specifically highlighting the importance of US for the COVID-19 epidemic, which includes both lung features, as well as significant comorbidities.

Most recently, physicians in Asia and Europe turned to US for detection and monitoring of lung abnormalities consistent with novel pneumonia and acute respiratory distress syndrome (ARDS) that are the hallmark of COVID-19 disease [28], [29]. The use of US has been proposed and studied for the detection and management of pneumonia in both pediatric [30], [31] and adult populations [6]. Recent studies have been published evaluating the utility of POCUS and general US for COVID-19 disease [29], [32], [33]. Lung US has been used during the COVID-19 pandemic in Asia [9] and also in Europe [10], [11].

A. Physics and Biology

The basis for the use of US in the detection and management of COVID-19 disease is the detection of inflammatory fluid "exudate" filling in alveolar sacs in the lung that lie immediately below the visceral pleura. As illustrated in Fig. 1, the lung is composed of a honeycomb structure of alveolar sacs within which oxygen and carbon dioxide are exchanged with blood flow to and from the heart [34]. Within these

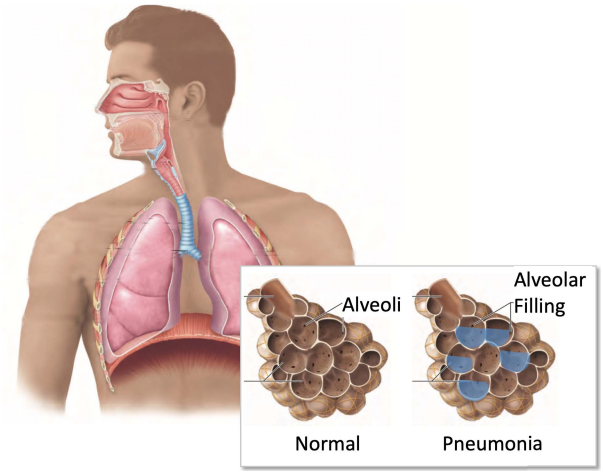


Fig. 1. Alveolar filling in pneumonia. Adapted from [35] and modified to show the filling of alveoli with waste fluid from an immune response that is indicative of pneumonia.

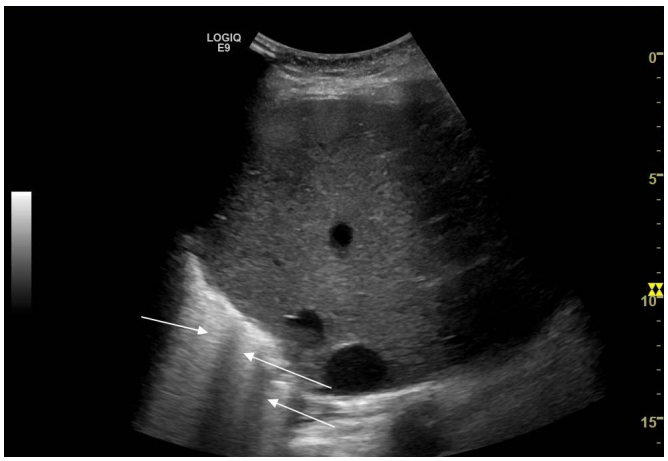


Fig. 2. Gray-scale longitudinal image of the liver in a patient with COVID-19 positive and abnormal liver function tests. The image of the liver includes the base of the right lung demonstrating the characteristic B lines seen in COVID-19 pneumonia (white arrows). Image provided by Prof. Hisham Tchelepi, Keck School of Medicine, University of Southern California (USC).

alveolar sacs, Type II pneumocytes, which are epithelial cells lining the surface of the sacs, are responsible for secreting surfactant that helps to maintain the sacs open and free of extraneous debris [35], [36]. These cells express a specific receptor for angiotensin-converting enzyme (ACE) 2 [37]. It is this ACE2 receptor that is the direct target of SARS-Cov2 [38], which forms a highly specific bond that then precipitates the entry of the viral RNA into the cell. Once the pneumocytes are infected with the viral RNA, they begin to produce a large number of copies of the virus that then spread further. As the body recognizes the increasing prevalence of viral copies, the immune system begins to attack them by initiating a cascade of proinflammatory immune signaling proteins (cytokines) that are responsible for recruiting the body's immune cells to attack foreign-identified structures (including Interleukin-1 and Interleukin-6). Products from the immune activity, which includes killed virus-infected cells, begin to fill the alveoli, which, in turn, compromises their ability for gas exchange [39], [40]. This condition of filled alveoli is related to pneumonia [34] and can be visualized indirectly using US.

B. Alveolar Filing Indicated by "B-Lines"

An important feature of lung US is the fact that much of the diagnostic information that is available to the physician comes in the form of interpretation of US artifacts in the acquired images. The main reason for this is that US is highly reflected at the boundary between tissue and air, and therefore, the lung is not ordinarily accessible. However, there are certain disease states that it has been established can be inferred based on visual vertical US artifacts in the lung. These include fibrosis, lung contusions, and pneumothorax, as well as viral and bacterial pneumonia [6], [41]–[43]. The observation of so-called vertical "B-lines" in the image [44] is indicative of pneumonia as evidenced by interstitial disease [30]. These appear as long vertical rays in the image (see Fig. 2). Normally, the US beam is unable to penetrate the air-filled alveoli due to acoustic reflection at the tissue air interface. In the presence of fluid within the alveoli secondary to an infection, however, the US beam is able to be transmitted across the pleural line into the fluid, and thus, a B-line in the image is formed [44]. The US is then caught between the deeper alveoli that are still filled with air and the visceral pleura that forms a resonance chamber [41], [42]. Some of the sound leaks out of this cavity and returns to the US system, and with each transmit cycle, additional acoustic energy is coupled into the resonance chamber. It is important to understand that these long vertical B-lines are not penetrating the lung parenchyma; they can only penetrate as deep as there is interstitial fluid filling. However, the ringing within these persists well into the receive cycle and is, therefore, interpreted by the beamformer as a long, vertically radiating line in the image [42]. There is some indication that the presence of B-lines in the image is influenced by the probe frequency [41].

C. Scanning Protocol

A number of protocols for lung scans have been developed, and among them, the BLUE protocol is used [6]. This consists of a set series of scans conducted by positioning a linear array or curvilinear array either straddling the intercostal space, or lying in a transverse position, parallel to the ribs in the intercostal space. Fig. 3(a) provides a diagram that shows, for example, four prescribed BLUE protocol scanning points that are used during the assessment (circles with target markings). Low-frequency settings (3–5 MHz) are used to increase the penetration of sound into the lung [41]. The goal of lung US is to visualize image artifacts, and therefore, compounding is not used [11]. According to the BLUE protocol, multiple scans are conducted at specific points on the front and back of the chest and also on the sides right below the armpit. The presence of lung consolidation (fluid-filled alveoli) can also be observed because it results in an aggregation of filled alveoli that can then propagate sound much deeper into the lung. This feature appears as a structured region below the

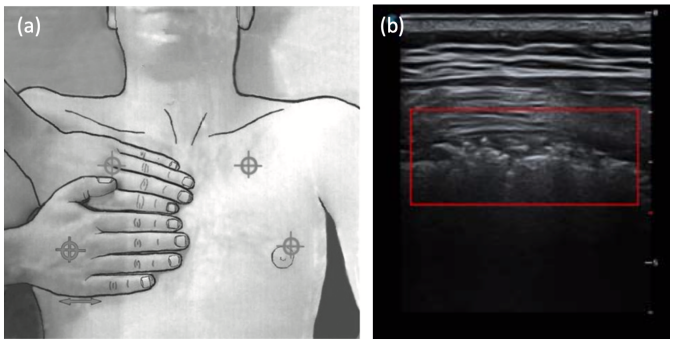


Fig. 3. Lung US for COVID-19. (a) Blue protocol points adapted from [83] and (b) lung consolidation (area internal to the red box) due to COVID-19 pneumonia visualized by US, adapted from [9].

pleural line (see Fig. 3(b), the complex area inside the red box) and is indicative of advanced disease [9]. Researchers have published a system for scoring and rating the progression of disease utilizing US [11].

The use of US for detection and monitoring of COVID-19 disease, therefore, relies on previously established protocols and procedures for detection and diagnosis of viral and bacterial pneumonia [6], [9], [43]. Their use is facilitated by the wide variety of portable and handheld US devices that have been introduced in recent years [11], [32]. Further adoption of US for COVID-19 will be driven by the utility of inexpensive and portable devices that are readily embedded in an isolated ICU and can be brought directly to the bedside of the affected patients [11].

D. Comorbidity Factors of COVID-19

Clinical experience during the COVID-19 pandemic has indicated that significant associated morbidity arises due to the progression of comorbidities that are not lung-specific [24], [45], [46].

Especially, circulatory disease (hypertension and heart disease), endocrine disease, kidney failure, and liver damage have all been implicated.

Circulatory disease, including hypertension and coronary heart diseases, remains the most common baseline comorbidity. In a case series of 21 patients with COVID-19, congestive heart failure was found to be the second most common baseline comorbidity (42.9%) [24]. A recent review of the potential effects of coronavirus on the cardiovascular system found that COVID-19 can cause heart injury, even in people without underlying heart issues [47]. In addition to circulatory disease, patients with COVID-19 may also suffer from an endocrine disease, kidney failure, and liver damage as suggested by a recent investigation that evaluated the impact of comorbidities [45].

Compared with CT or CXR that are mainly focused on the patients' lungs themselves, most of the comorbidity factors of COVID-19 can be diagnosed using the standard US. More specifically, cardiac US imaging is widely implemented to aid in the clinical diagnosis of many cardiovascular diseases using Doppler imaging, contrast echocardiography, point-of-care echocardiography, and so forth [48]. Abdominal US imaging is another widely used imaging technique to diagnose organs in the abdomen, including the liver, spleen, pancreas, and kidney [49]. The blood vessels that lead to some of these organs, such as the inferior vena cava and aorta, can also be evaluated using US [49].

Therefore, US can serve a dual role by assessing the severity of lung involvement, as well as the management of extrapulmonary manifestations of the disease process, which are detrimental to patient outcomes [39].

III. US Transducers Probes for COVID-19

This section provides a brief review of the use of standard US probes for lung and COVID-19. The US transducer is the most important component of the US imaging system, and its performance is critical to the quality of the US image. In general, the transducer translates electrical impulses into sound waves, and sound waves scattered by the imaged subject are, in turn, detected as returning echoes that are then converted back to electrical signals for processing by the system. In terms of depth of penetration, resolution, and other application-driven requirements, there is a range of transducers used, from a single element to array transducers with hundreds or thousands of elements. Researchers and physicians have attempted to address the question of which of these commonly used general imaging probes is optimal for lung imaging [50]. The second question that has been investigated is that of the optimal center frequency for lung imaging [51].

The selection of probe type for pneumothorax in the lung has been assessed by Ketelaars *et al.* [50]. In their analysis, they concluded that there was no difference in diagnostic performance among linear arrays, curved linear arrays, and phase array in lung US. Based on image quality, the linear array transducer might be preferred for lung ultrasonography for examining the pleural line due to its higher image resolution, which is important for assessing fine features. However, due to the position of the lung, a small footprint convex probe is best suited because it can be placed easily in the intercostal space.

At present, there is no specific US frequency for assessment of the lung. In general, a low-frequency transducer in the range of 3–5 MHz is useful in the assessment of effusions, consolidations, and extension of B-lines [43]. Probes in the range of 6–13 MHz, which have higher image resolution, are preferred for imaging the pleura and lung sliding. Adhikari [51] also indicated that 5–10-MHz transducers are adequate to obtain images that can be used for medical decision-making for a variety of POCUS applications, including lung ultrasonography.

There is some indication that the generation of B-lines is frequency-dependent [27] with higher frequencies in the range above 4 MHz being preferred, while, at the same time, convex probes with low frequency, such as are standard for abdominal imaging, are preferred for imaging deep structures that can indicate lung consolidation [52]. Higher frequency linear arrays (3–17 MHz) can also be useful for monitoring changes in subpleural lesions [53]. The frame rate of the imaging and focal point location has also been proposed as important

considerations with a higher frame rate being beneficial and setting the focal point at the pleural line being important [11]. Therefore, a tradeoff between penetration depth that favors low frequencies and image resolution and B-line generation favoring higher frequencies suggests that a wide bandwidth probe may be beneficial for general use in COVID-19.

IV. Portable US in COVID-19

An international group of physicians and researchers recently published a proposal for standardization of the use of lung US for COVID-19 patients [11]. The goal of this effort was to establish a simple, quantitative, and reproducible method for COVID-19 diagnosis using US. In the proposal, it was indicated that physicians should avoid the use of specialized image processing filters and specific image settings, such as harmonic imaging, contrast-enhanced imaging, and color Doppler imaging. Useful US findings for COVID-19 primarily rely on imaging the pleural line, B-lines, and consolidations using conventional US B-mode imaging. This protocol relaxes the requirements for both hardware and software in US machines used for COVID-19 disease management, which, in turn, should facilitate the application of less complex systems that are miniaturized and highly portable. Some pioneering studies have shown the benefits of portable US devices for diagnosing respiratory illnesses while maintaining proper isolation protocol [11], [29], [32], [33].

Portable and handheld US imaging systems used for POCUS diagnostic imaging systems benefit from being safe, affordable, portable, and easy to use [25]. The use of portable US systems that can be brought directly to the patient bedside in the ICU can reduce the work required for transferring patients from the ICU to the radiology department to be imaged with CT. Also, reducing the need to transfer patients from the ICU can significantly reduce cross-infection with other patients in the hospital and non-COVID-19 staff. Conventional US imaging systems can be moved relatively easily compared with MRI systems and CT systems, and portable and handheld US imaging systems further reinforce this advantage when facing a large number of COVID-19 patients. Portable and handheld devices can be easily transported to different rooms within the hospital to evaluate potential lung involvement. In practice, handheld US devices have been used to detect B-lines in lung conditions [54]. In addition to improvements in hardware and algorithms, continuous advances in smartphone and tablet technologies can also bring improvements in image quality, display performance, and archiving capabilities for these highly portable systems, with the goal being performance eventually rivaling traditional cart-based machines. The high-performance hardware and mature operating systems in modern powerful smartphones and tablets provide significant benefits for POCUS imaging systems for COVID-19 diagnosis.

Ahn *et al.* [55] described a US imaging system based on an android-OS smartphone, which achieved real-time B-mode imaging with a sufficient frame rate (i.e., 58 frames/s). The battery life for POCUS diagnosis for their device was 54 min without charging. The use of a standard USB 3.0 interface ensured that data could be transferred and processed in real time. Handheld US probes have been developed, which takes advantage of the powerful data processing and image display capabilities of modern smartphone and tablet computers, showing promise for POCUS [25].

Fig. 4. Example portable handheld US machines. (a) Vscan by GEHealthcare. (b) Butterfly iQ by Butterfly, Inc. (c) Freestyle by Siemens Healthineers. Downloaded from GE, Butterfly, and Siemens websites.

A range of handheld and portable units have recently been introduced into practice by major US equipment manufacturers. Fig. 4 shows currently available portable and handheld US machines manufactured by: 1) GE healthcare; 2) Butterfly Inc; and 3) Siemens Healthineers. Each of these units houses beamforming electronics in the probe handle itself. These highly portable handheld devices benefit from intensive efforts to integrate the electronic beamforming functionality of US into increasingly smaller chipsets and form factors [15], [16]. Wireless probes remove the cable between the probe and the system processing unit and display [56], making them convenient for carrying by the physician and may eventually replace the stethoscope as the standard of care in the ER and ICU for both traditional use [56], [57] as well as for COVID-19 specifically [58].

Handheld portable US systems allow doctors and nurses to monitor the state of illness of patients in the ICU instead of moving them outside, which avoids the spread of disease. In addition, management and diagnosis of COVID-19 in the ICU must take into account the health of the physicians and nurses who are caring for these patients. With this in mind, a protocol for standardization of the use of POCUS for COVID-19 has been proposed as follows [58]: The primary physician holds the US probe and acquires images, while an assistant operates the system console or interface tablet (i.e., to adjust parameters, store images, and so on), without contacting the patient or the US probe, to avoid the potential for cross-infection. If necessary, the second physician can be located outside the ICU or ward. The second physician can communicate and monitor the screening test using a wireless tablet with the physician besides the patient, resulting in less operator dependence of the imaging procedure.

With the advent of increasingly integrated beamforming and signal processing electronics [15]–[17], multiple portable and wireless US imaging probes and systems have been fabricated for handheld applications [56], [59]–[62]. One of the limitations that constrain the further progress of these handheld probes is the power consumption of the electronics [56]. To address this challenge and realize low-power high-performance handheld imagers, microchip

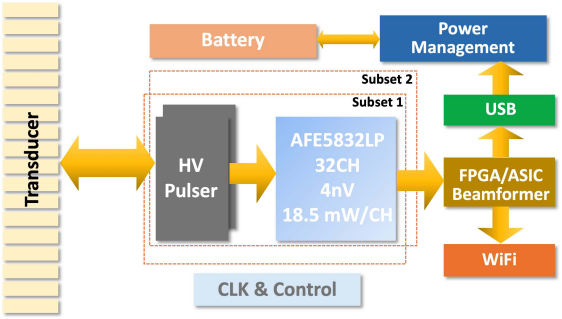


Fig. 5. Block diagram of a typical wireless US probe implemented using a highly integrated AFE ASIC device. Adapted from [16].

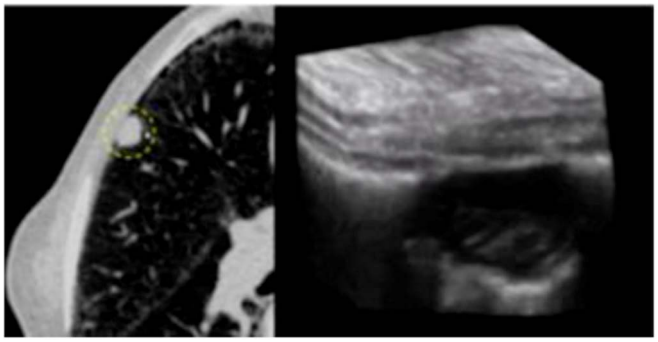


Fig. 6. Use of 3-D US for lung [26].

vendors, including Texas Instruments (TI) and Analog Devices (ADI), have released complete analog front-end (AFE) systems on a chip for processing US transducer signals at high density and low power [15], [16]. Fig. 5 provides a block diagram of the implementation of a portable US system using the AFE5832LP device [16] that is a 32-CH AFE solution for operation with low power. This device consumes 20 mW per channel, which is six times lower than AFE devices in conventional console systems. The sampling frequency of the ADC is selectable up to four times higher than the probe frequency for 10-MHz operation. The time–gain–compensation (TGC) circuits are integrated on-chip, which simplifies the system-level design and reduces overall probe power consumption. Digitized data can be combined using on-chip digital encoders and transmitted on a single LVDS differential output pair at up to 1 Gb/s. The standard power consumption of the device is 0.6 W, constituting about 20% of the total power consumption in a typical handheld US implementation. For lung imaging, in particular, an important constraint is a reduction of transmit power when imaging parenchymal tissue [63], and this is also beneficial for a portable application because it reduces drain on the battery.

Another constraint comes from the data transfer. Due to size limitations, the high-speed data buses that are commonly used in conventional systems, such as peripheral component interconnect express (PCIe), are not applicable for handheld devices. Instead, USB is widely used for handheld devices and has been used in the portable Acuson P10 system by Siemens Medical Solutions, GE Healthcare VScan, and Butterfly's iQ [62]. With the latest USB 3.0 technology, images with higher resolution and frame rates should be available in the near future. Another important feature of newly available portable systems is the use of wireless data. For example, the Clarius system [62] offers this feature. Without the constraint of the cable, the device can be even more convenient for doctors and nurses to use at the patient's bedside; however, the power consumption will be higher, and the devices cannot be charged by the display console.

V. Future: 3-D US Imaging and Novel Transducers Technologies

To date, the most applicable technology for ultrasonic arrays for diagnosis and management of COVID-19 disease and comorbidities has been 1-D arrays in the clinical frequency ranges of 3–5 MHz [43], and also, POCUS has shown promise in this regard [29], [32], [33]. However, newer systems on the horizon hold promise for improved imaging of the lung, and these include novel portable 3-D imaging devices, as well as novel high sensitivity transducer technologies and imaging algorithms to improve data interpretation. These are discussed, in turn, in this section in the following.

A. Volumetric Imaging–2-D Arrays

As opposed to the standard 1-D array systems, the use of a large aperture 2-D array [64] that, instead, acquires volume image data spanning a larger imaging area has the potential to accelerate the imaging procedure time for each patient by acquiring multiple views similar to techniques that have recently been proposed for operator-independent assessment of pneumonia [65]. This could reduce the time for assessing patients on triage, which could improve throughput for high-volume hospitals during the pandemic.

The application of volumetric arrays to adult and pediatric lung imaging has been previously investigated [26], [65]. The use of swept volumes was investigated for reducing the variability of lung US in rural areas for the detection of pneumonia [65]. A 2-D array for the evaluation of pleural lesions and pulmonary nodules was also investigated [26] (see Fig. 6). With the advancement of 2-D array technologies in recent years [66]–[68], there remains a significant opportunity for a new investigation to further evaluate utility for lung.

Significant work in the past two decades has been undertaken to create enabling technologies for the implementation of 2-D arrays [17], [66]–[73]. Some of these arrays use integrated circuits (ICs) to greatly reduce the required footprint and power for signal processing to implement 2-D array beamforming for volumetric data acquisitions. Other arrays implement sophisticated beamforming algorithms that realize savings in the number of channels used. Microbeamformers have been implemented to efficiently partition the beamforming process and, thereby, greatly reduce the number of cables and power needed for 2-D array scanning [17], [66], [67]. Row–column arrays have been implemented to take advantage of redundancies in the beamforming process to greatly reduce the number of channels necessary for implementing 2-D array sampling [70], [71], [73]. Multiplexed arrays

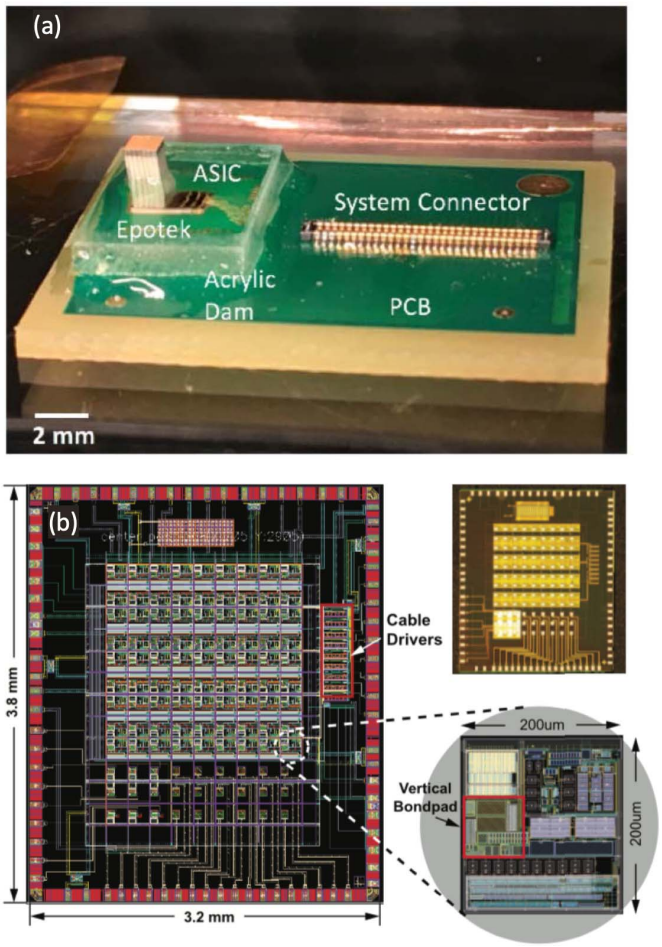


Fig. 7. ASICs for 2-D array implementations. (a) 40-channel multiplexed array at a 300-μm pitch and a 5-MHz center frequency by Thomenius *et al.* [68]. (b) Receive matrix ASIC with low-power microbeamforming delay line *Chen et al.* [17].

use ICs to reduce the number of required system channels by selecting different groupings of elements for 2-D array beamforming [68], [69], [74].

As an example of the recent work for 2-D arrays, Wodnicki *et al.* [68] implemented a 300-μm-pitch IC matched to a PIN-PMN-PT material transducer array for a 2-D array with modular tiling by the direct assembly of an acoustic stack using a 3-D printed backing interposer [see Fig. 7(a)]. The device had a bandwidth of 77% operating at the 4.55-MHz center frequency. Chen *et al.* [17] implemented a 2-D array matrix transducer with integrated receive ASIC that had a 9 $\times$ 12 matrix of receive elements and was realized in a 0.18-μm CMOS process [see Fig. 7(b)]. The array achieved a dynamic range of 77 dB and operated at a center frequency of 5 MHz. Jung *et al.* [74] implemented a 1:64 channel high-voltage multiplexing ASIC for ultrasonic applications with an ON-resistance of 140 Ω. The device is intended for greatly reducing the number of cables needed to process an array of elements by using synthetic aperture techniques to successively select the required channels for beamforming.

For COVID-19-related applications, the frequency of imaging and bandwidth can be an important consideration [52], [53]. The pitch of elements in US is directly related to the operating center frequency with linear and curvilinear arrays typically designed for λ pitch [76]. In addition, a wide bandwidth transducer (see Section V-B) can provide a greater range of operating frequencies, which will be beneficial for trading off penetration, image resolution, and B-line generation without the need for exchanging probes.

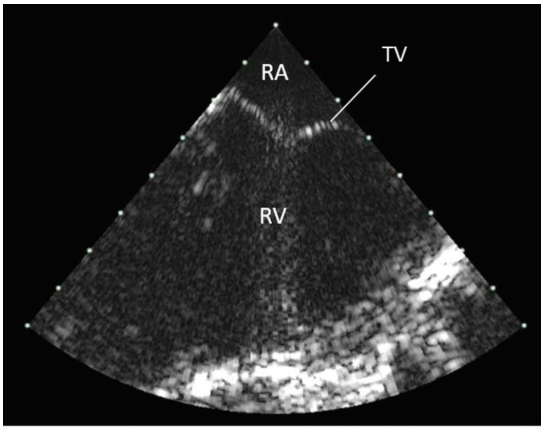
To realize the true benefit of 2-D volumetric arrays for lung, it will be necessary to implement these probes in handheld POCUS systems. An important consideration in this regard is power consumption. For portable or even handheld 2-D US device, power consumption management will become a potential bottleneck. Butterfly Network's handheld US device is powered by a built-in battery. The run time is 120 min, and it takes up to 5 h to full recharge [62]. For a 2-D probe, considering the size and weight, a larger battery may not be applicable, which means that power management will be more challenging. New IC design technologies and batteries with higher energy density are a potential solution to this problem.

B. Novel Transducers: CMUT, PMUT, and PMN-PT

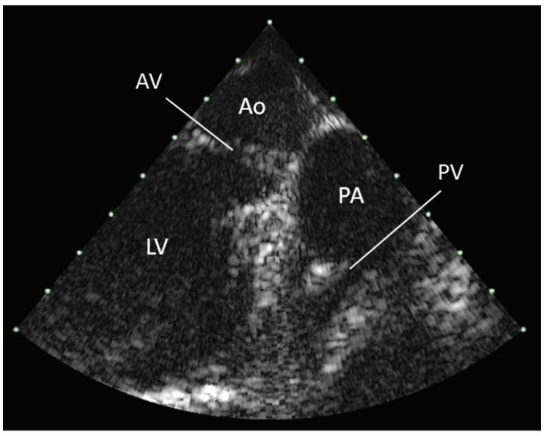
An important consideration for US probes, in general, is the improved sensitivity so that weaker signals can be efficiently detected for imaging. In addition, for use in lung and for COVID-19 lung assessment, a wide selection of imaging frequencies can be beneficial [27]. At the same time, for a widely disseminated diagnostic tool that can be used by many physicians in ICUs at the bedside of COVID-19 patients, high-volume production of US arrays can be an important consideration. All of these issues have been attempted to be addressed by novel transducer technologies that are fabricated using high-volume semiconductor manufacturing technologies. These so-called micromachined US transducers (MUTs) come in different varieties, as described in the following.

Capacitive micromachined ultrasonic transducer (CMUT) devices offer a superior method of US generation and detection and have been proposed for medical US imaging for a long time [72], [75], [77]. Transmit and receive operations of CMUTs are based on the flexural vibration of a thin diaphragm separated from a fixed backplate by a small gap. CMUT probes take advantage of the ease of fabricating small kerf widths using standard microfabrication techniques. Compared with traditional piezoelectric-based probes, CMUT probes have a number of advantages: wide bandwidth, easy volume fabrication, and high thermal efficiency. Kolo Medical Inc [78] presented a 15-MHz 256-element linear array US probe that was developed with CMUT technology and demonstrated its application for medical US imaging. Also, Savoia *et al.* [75] presented a 12-MHz US probe for medical imaging and showed the superiority of CMUT probes with respect to piezoelectric technology for both transmission and frequency responses. While these devices operate at a higher frequency, lower frequencies that are in the standard diagnostic range and, therefore, appropriate for use with COVID-19 have also been investigated [72].

Combining the technology of piezoelectric film deposition with MEMS technology enables the manufacture of piezoelectric MUTs (PMUTs). Dausch *et al.* [79] presented an



(a)



(b)

Fig. 8. *In vivo* b-mode images acquired using PMUT array operating at 5 MHz with the V360 system and positioned in the right atrium (RA) of a porcine model. (a) Image of the tricuspid valve (TV) and right ventricle (RV). (b) Image of the aorta (Ao), aortic valve (AV), pulmonary artery (PA), pulmonary valve (PV), and left ventricle (LV). Adapted from [79].

US transducer for intracardiac imaging using a 2-D PMUT array. This array has a rectangular aperture containing 256 × 512 elements with a center frequency of 5 MHz. The elements were accessed using through-silicon interconnects in the substrate of the PMUT array, which enables the integration of the high-density array with catheter cabling. The results of *in vivo* testing with a V360 system are shown in Fig. 8. These results demonstrate that PMUTs are a promising new technology for US imaging.

While MUT-based US systems hold great promise in terms of future commodity systems, current manufacturers have relied mainly on novel formulations of standard piezoelectric materials. Especially, the excellent performance of lead-based piezoelectric single-crystal materials has motivated many well-known multinational companies, such as Philips, GE, Siemens, Toshiba, and Hitachi, to develop PMN-PT single-crystal-based US probes [18], [80]–[82]. Vermon proposed to use the dice and fill technique for manufacturing a US probe based on 1-3 single-crystal composite materials [19]. The test results of this array showed that compared with piezocomposite transducers, it has better bandwidth and improvement of +6 dB in sensitivity.

C. New Imaging Techniques for Clearer Interpretation

Conventional US machines utilize either 1-D linear arrays or phased arrays to provide cross-sectional imaging, producing slices similar to CT and MR. However, acquisition and interpretation of these 1-D US images, in general, are highly operator-dependent, and physicians must follow a prescribed and time-consuming protocol to examine the whole lung [65], [83]. To reduce the challenges of interclinician or intraclinician variabilities, US-based computer-aided diagnosis has been shown to be a powerful tool in certain applications, including breast [84]–[86] and thyroid [87]. A pioneering study localizing B-lines in lung US using deep learning methods has been reported [88], which may guide the future direction of US technology for COVID-19.

In addition to conventional US imaging that only provides morphological tissue information, US elastography is a newly developed imaging technique that uses either mechanically generated vibrations or ultrasonically generated acoustic radiation force (ARF) to assess the biomechanical properties of soft tissues, such as stiffness or elasticity. These mechanical properties have demonstrated predictive value in several applications, including the liver [89], breast [90], and thyroid [91]. Pioneering studies in the lung have also recently been demonstrated [92]; however, these did not use ARF as there is the potential for damage to the lung with acoustic forcing [63]. Elastography methods [93], [94] for tissue property assessment could also be combined with 2-D array probes [26], [64], [65] to further improve the specificity of US for COVID-19 lung condition assessment. There are also additional methods of lung tissue characterization based on the assessment of the frequency domain and multiple scattering properties of the lung parenchyma that hold promise for evaluation of the physical disease state of the lung [27], [95].

VI. Conclusion

In this article, we have reviewed existing and future technologies for the potential use of US for diagnosis and management of the novel COVID-19 lung illness. This condition is especially challenging for physicians and health systems due to its multiple comorbidities and refractory primary disease. Clinicians are forced to consistently balance the requirements for obtaining useful information for critical treatment decisions, with the need to maintain isolation of themselves and COVID-19-negative patients. US holds great promise in this regard, due to the fact that is it highly versatile, portable, and inexpensive, while, at the same time, being applicable across a broad spectrum of conditions. With multiple expected waves of this disease pandemic, there exists a critical need to streamline the work of physicians, providing tools to increase the ability to quickly diagnose and treat the primary condition as well as comorbidities. New technologies, such as US arrays with a wide frequency range, computer-aided diagnosis, and 2-D arrays producing volumetric images, should be further investigated to establish their utility for COVID-19.

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Xuejun Qian (Member, IEEE) received the B.S. degree in electrical engineering from Xidian University, Xi'an, China, in 2012, and the M.S. degree in electrical engineering and the Ph.D. degree in biomedical engineering from the University of Southern California, Los Angeles, CA, USA, in 2014 and 2018, respectively.

He joined the NIH Ultrasonic Transducer Resource Center (UTRC), University of Southern California, as a Research Assistant, under the supervision of Dr. Qifa Zhou and Dr. K. Kirk Shung. His research interests include high-frequency ultrasound elastography, optical coherence elastography, super-resolution microvessel imaging, and multimodality imaging.

Robert Wodnicki (Member, IEEE) received the B.Eng. and M.Eng. degrees in electrical engineering from McGill University, Montreal, QC, Canada, in 1992 and 1996, respectively. He is currently pursuing the Ph.D. degree in biomedical engineering with the University of Southern California, Los Angeles, CA, USA.

From 1995 to 2014, he was an ASIC Designer with GE Global Research, Niskayuna, NY, USA. His research is focused on the implementation of 2-D ultrasound systems utilizing highly integrated ASIC electronics interfaced to single-crystal transducer arrays.

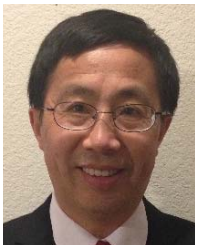
Haochen Kang (Graduate Student Member, IEEE) received the B.Eng. degree in electrical engineering from the Huazhong University of Science and Technology, Wuhan, China, in 2015, and the M.S. degree in electrical engineering from the University of Southern California, Los Angeles, CA, USA, in 2017, where he is currently pursuing the Ph.D. degree in biomedical engineering.

His research is focused on the design and application of 2-D ultrasound systems.

Junhang Zhang was born in April 1993. He received the M.S. degree in biomedical engineering from the University of Southern California, Los Angeles, CA, USA, in 2020, where he is currently pursuing the Ph.D. degree with the Department of Biomedical Engineering.

His current interests include the development of high-frequency transducer and ultrasonic elastography.

Hisham Tchelepi was the Director of Ultrasound with the School of Medicine, Wake Forest University, Winston-Salem, NC, USA. During his tenure at Wake Forest University, he worked with a manufacturer on improving and developing new technologies in diagnostic ultrasound. In November 2013, he joined the Department of Radiology, Keck School of Medicine, University of Southern California (USC), Los Angeles, CA, USA, to head the Ultrasound Section. He is also a leader in the field of fusion ultrasound with computed tomography (CT)/magnetic resonance (MR) and positron emission tomography (PET) imaging. His expertise evolved into improving the means of interventional procedures performed under ultrasound guidance minimizing radiation dose to patients and operators alike. He lectured about this technology both nationally and internationally. He was invited to many academic institutions as a visiting professor to share his expertise and knowledge. He is dedicated to residents' education and has been selected as a teacher of the year both at USC and Wake Forest University. His research has focused on the improvement of image quality and contrast sonography. He is the author of numerous book chapters and one book. He reviews many major radiology and ultrasound journals. He worked on some of the topics of ultrasound with the American College of Radiology Appropriateness Criteria. Currently, his interest is focused on the role of elastography in evaluating the degree of fibrosis in chronic liver disease as well as the use of contrast ultrasound in evaluating liver and hepatic masses.



Qifa Zhou (Fellow, IEEE) received the Ph.D. degree from the Department of Electronic Materials and Engineering, Xi'an Jiaotong University, Xi'an, China in 1993.

He is currently a Professor of biomedical engineering and ophthalmology with the University of Southern California, Los Angeles, CA, USA. He has published more than 280 peer-reviewed articles in journals and edited two books. His research focuses on the development of piezoelectric high-frequency ultrasonic transducers/array for the biomedical ultrasound and photoacoustic imaging, including intravascular imaging, elastography, and ophthalmic imaging. He is also actively exploring ultrasonic mediated therapeutic technology, including transsclera drug delivery, as well as ultrasound for retinal and brain stimulation.

Dr. Zhou is also a fellow of the International Society for Optics and Photonics (SPIE) and the American Institute for Medical and Biological Engineering (AIMBE). He is also a member of the Technical Program Committee of the IEEE International Ultrasonics Symposium. He is also an Associate Editor of the IEEE TRANSACTIONS ON ULTRASONICS, FERROELECTRICS, AND FREQUENCY CONTROL.