

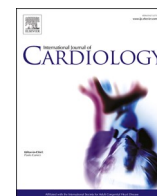


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Short communication

Echocardiography in the time of Covid-19: Ultrasound enhancing agents save time and augment diagnostic information

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ABSTRACT

Background: There are currently no clear guidelines regarding the use of ultrasound enhancing agents (UEAs) with transthoracic echocardiography (TTE) for patients hospitalized with Covid-19. We investigated whether the performance of TTE with UEAs provides more diagnostic information and allows for shorter acquisition time compared to unenhanced TTE imaging in this patient population.

Methods: We analyzed the TTEs of 107 hospitalized Covid-19 patients between April and June 2020 who were administered UEAs (Definity®, Lantheus). The time to acquire images with and without UEAs was calculated. A level III echocardiographer determined if new, clinically significant findings were visualized with the addition of UEAs.

Results: There was a mean of 11.84 ± 3.59 UEA cine-loops/study vs 20.74 ± 8.10 non-UEA cine-loops/study ($p < 0.0001$). Mean time to acquire UEA cine-loop images was 72.28 ± 28.18 s/study compared to 188.07 ± 86.04 s/study for non-UEA cine-loop images ($p < 0.0001$). Forty-eight patients (45%) had at least one new finding on UEA imaging, with a total of 62 new findings seen. New information gained with UEAs was more likely to be found in patients with acute respiratory distress syndrome (21 vs 9, $p < 0.001$) and in those on mechanical ventilation (21 vs 15, $p = 0.046$).

Conclusions: TTE with UEAs required less time and fewer cine-loop images compared to non-UEA imaging in patients hospitalized with Covid-19. Additionally, Covid-19 patients with severe respiratory disease benefited most with regard to new diagnostic information. Health care personnel should consider early use of UEAs in select hospitalized Covid-19 patients in order to reduce exposure and optimize diagnostic yield.

1. Introduction

Myocardial injury as evidenced by an abnormal transthoracic echocardiogram (TTE) is strongly associated with increased mortality in hospitalized patients with Covid-19 [1]. However, TTE studies performed on these patients are frequently technically challenging with ensuing longer acquisition time and limited diagnostic information, especially in patients with severe respiratory dysfunction and/or requiring mechanical ventilation. Limiting sonographer and physician exposure to Covid-19 is important in mitigating community and nosocomial spread. Thus, in patients with Covid-19, it is crucial to expedite

TTE performance time while simultaneously prioritizing diagnostic accuracy. Ultrasound enhancing agents (UEAs) have been shown to improve endocardial resolution and provide diagnostic images in technically limited studies [2]. Current guidelines from the American Society of Echocardiography recommend that UEAs should be considered in Covid-19 patients if the administration of UEAs will be beneficial with regard to diagnostic yield and scan time [3]; however, this has yet to be shown. In this study, we sought to determine if UEAs increase the diagnostic yield of TTEs in hospitalized Covid-19 patients, to identify patient subsets that benefit most from UEAs, and to quantify the time required to obtain images with UEAs compared to unenhanced images.

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¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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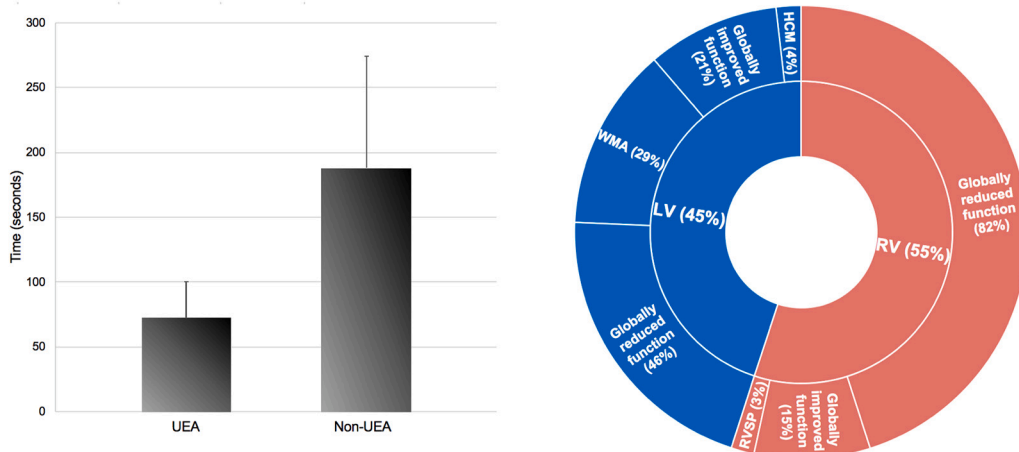


Fig. 1. Mean acquisition time for UEA compared to non-UEA cineloop images (left), and breakdown of new findings from UEA imaging (right). WMA: wall motion abnormality; HCM: hypertrophic cardiomyopathy; RVSP: right ventricular systolic pressure.

2. Methods

We performed a single center retrospective study of hospitalized adult patients between April and June 2020 who tested positive for Covid-19 via nasal swab polymerase chain reaction and who underwent TTE. UEAs (Definity®, Lantheus) were administered in 86% of TTEs completed on this cohort of patients. A level III echocardiographer, blinded to all clinical data, analyzed 107 consecutive TTEs that had UEAs administered immediately following unenhanced imaging to determine if new, clinically significant findings were found with UEAs. A new finding was defined as improved or reduced global left ventricular (LV) and/or right ventricular (RV) function, a new regional wall motion abnormality, and/or better quantification of right ventricular systolic pressure (RVSP) previously not seen on the non-UEA cineloops. We analyzed the time to acquire long, short, apical, and subxiphoid imaging planes with and without UEAs and excluded the time needed for Doppler and M-mode images. A student *t*-test compared the mean total time per study and number of cineloop images with and without UEAs.

3. Results

Of the 107 patients (66% male; mean age 58.7 ± 15.6 years; mean BMI 28.9 ± 8.1; 12.1% with history of heart failure; 9.3% with history of atrial arrhythmia), fifty-one (47.7%) patients were in the intensive care unit (ICU), thirty (28.0%) patients had a diagnosis of acute respiratory distress syndrome (ARDS), thirty-six (33.6%) patients were mechanically ventilated, and thirty-four (31.8%) patients were in shock. The average left ventricular ejection fraction on TTE was 55% ± 14.2. The studied patients had a mortality rate of 24% during their hospitalization.

There was a mean of 11.8 ± 3.6 UEA cineloops/study vs. 20.7 ± 8.1 non-UEA cineloops/study (*p* < 0.0001). Mean time to acquire all UEA cineloop images was 72.3 ± 28.2 s/study compared to 188.1 ± 86.0 s/study for non-UEA cineloop images (*p* < 0.0001) (Fig. 1). With regard to diagnostic information, forty-eight patients (45% of the cohort) had at least one new finding on UEA imaging that was not visualized on non-UEA imaging. A total of 62 new findings were seen amongst all patients: 28 (45%) were related to the LV and 34 (55%) were related to the RV (Fig. 1). Of the new LV findings, UEAs clarified that 21.4% had a global improvement in function, 46.4% had a global decrease in function, and 28.6% had a newly visualized wall motion abnormality. Additionally, one patient had newly identified hypertrophic cardiomyopathy. Of the new RV findings, 14.7% had a global improvement in function, 82.4% had a global decrease in function, and there were no newly visualized wall motion abnormalities. One patient had better quantification of RVSP with UEA. In total, globally reduced LV and/or

Table 1

Patients with and without new TTE findings upon utilization of UEA, subdivided by clinical status.

Clinical status	Patients with New UEA Finding		p-value
	Yes (N = 48)	No (N = 59)	
ICU care	24 (50.0%)	27 (45.8%)	0.60
ARDS	21 (43.8%)	9 (15.3%)	<0.001
Mechanical ventilation	21 (43.8%)	15 (25.4%)	0.046
Shock	19 (39.6%)	15 (25.4%)	0.12
Renal replacement	5 (10.4%)	8 (13.6%)	0.62
Suspected PE	3 (6.3%)	5 (8.5%)	0.66
Elevated troponin	14 (29.2%)	27 (45.8%)	0.08
Death during hospitalization	14 (29.2%)	12 (20.3%)	0.29

RV function comprised 66% of the new findings across the entire cohort. Notably, new information derived through the use of UEAs was more likely to be found in patients with ARDS (21 vs 9, *p* < 0.001) and in those on mechanical ventilation (21 vs 15, *p* = 0.046) (Table 1).

4. Discussion

We found that diagnostic TTE with UEAs required 62% less time and 43% fewer cineloop images compared to non-UEA imaging in patients hospitalized with Covid-19. Additionally, use of UEAs resulted in new findings for nearly half the patients in this cohort. In particular, the patients who benefited most from the administration of UEAs were those with ARDS and those requiring mechanical ventilation. UEA administration may be most beneficial in this subset of patients as optimal positioning of patients is typically difficult in those with ARDS on mechanical ventilation (90% of ARDS patients required mechanical ventilation in this cohort). Covid-19 patients' oxygenation status is very sensitive to exertion and positioning, and fibrotic lung with poor echogenicity can lead to difficult acoustic windows. Thus, UEAs would be of greater utility in this cohort of patients.

While the benefits of contrast echocardiography in critically ill and ICU patients has been shown previously [3–5], to our knowledge, this is the first study to illustrate its advantages of increased diagnostic yield in the hospitalized Covid-19 population. Additionally, UEAs have been shown to be safe in Covid-19 patients. A study by Argulian and colleagues illustrated that there were no adverse events seen within one hour after administration of UEAs in 33 patients hospitalized with Covid-19 [6]. Therefore, in this patient population, health care personnel could prepare UEAs in advance, prior to entering the patient's room, and consider early administration of UEAs in order to reduce

personnel exposure to Covid-19 while simultaneously optimizing diagnostic yield.

4.1. Limitations

Our study has a number of limitations. There were only a small number of subjects (14%) in our studied population without UEAs administered, likely due to all of the studies being performed at the bedside with patients' respiratory status creating technical challenges. This could represent a selection bias that might overestimate the added value of UEAs. Additionally, an inter-observer analysis was not performed.

5. Conclusion

Our results suggest that administration of UEAs in hospitalized Covid-19 patients provides new, clinically significant diagnostic information, particularly in patients with severe pulmonary disease. We hope that these findings will streamline identification of Covid-19 patients in whom administration of UEAs would be of greatest utility.

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References

- [1] G. Giustino, L.B. Croft, G.G. Stefanini, et al., Characterization of myocardial injury in patients with COVID-19, *J. Am. Coll. Cardiol.* 76 (18) (2020) 2043–2055.
- [2] M. Kurt, K.A. Shaikh, L. Peterson, et al., Impact of contrast echocardiography on evaluation of ventricular function and clinical management in a large prospective cohort, *J. Am. Coll. Cardiol.* 53 (9) (2009) 802–810.
- [3] ASE Statement on COVID-19, American Society of Echocardiography. <https://www.asecho.org/ase-statement-covid-19/>, 2021. Accessed April 10, 2021.
- [4] A.N. Makaryus, M.E. Zubrow, L.D. Gillam, et al., Contrast echocardiography improves the diagnostic yield of transthoracic studies performed in the intensive care setting by novice sonographers, *J. Am. Soc. Echocardiogr.* 18 (2005) 475–480.
- [5] Y. Yong, D. Wu, V. Fernandes, et al., Diagnostic accuracy and cost-effectiveness of contrast echocardiography on evaluation of cardiac function in technically very difficult patients in the intensive care unit, *Am. J. Cardiol.* 89 (2002) 711–718.
- [6] E. Argulian, K. Sud, C. Bohra, B. Vogel, V. Garg, S. Talebi, S. Lerakis, J. Narula, Safety of ultrasound enhancing agents in patients with covid-19, *J. Am. Soc. Echocardiogr.* 33 (7) (2020) 906–908.