Should “Cardiopulmonary Resuscitation–associated Lung Edema” Be Diagnosed More Cautiously?

To the Editor:

“Cardiopulmonary Resuscitation–associated Lung Edema (CRALE). A Translational Study” by Magliocca and colleagues (1) is commendable and contributes greatly to the field. We agree with the authors’ opinion on the presence of CRALE in animals and in patients with out-of-hospital cardiac arrest (CA). However, we wonder whether baseline disease severity and the etiology of CA had affected their evaluation of CRALE with respect to manual and mechanical chest compressions (CCs)—in particular, whether a patient had respiratory insufficiency before CA, which is the second most common cause (15–40%) of CA (2).

First, it is known that baseline organ function may directly contribute to injury and clinical outcomes after resuscitation (2). However, Magliocca and colleagues did not describe the baseline respiratory function of their 52 patients, nor did they evaluate the number and proportion of patients in whom CA was caused by respiratory insufficiency by comparing pre- and post-CA results with radiological examinations and arterial blood gas tests. Thus, computed tomography (CT) scans of lung edema within 24 hours after CA may have included those patients with pre-CA respiratory insufficiency, thereby increasing the study’s false-positive rate for CRALE. This hypothesis is supported by our preliminary retrospective study, in which we analyzed the data for patients with in-hospital CA admitted to the Fourth People’s Hospital of Zigong from July 6, 2012, to July 5, 2019. A total of 2,460 patients with in-hospital CA were recruited, of whom 173 underwent lung CT or X-ray examination both before and after CA. Of those patients, 25.43% (44/173) had post-CA lung edema that would have been diagnosed as CRALE per the evaluation criterion by Magliocca and colleagues. However, six of the patients also had pre-CA lung edema, which would have yielded a false-positive rate of 3.4% (6/173) for CRALE. Therefore, we believe it is not reasonable to diagnose CRALE based only on lung CT scans performed within 24 hours after CA. Therefore, we believed the changes between pre- and post-CA radiological results might be more qualified as the indicator for diagnosing CRALE.

Second, severe disease can increase the risk of serious organ dysfunction after resuscitation. In the study by Magliocca and colleagues, disease severity appeared to have been unbalanced between the mechanical and manual CC groups: the low-flow time was much longer in the mechanical CC group than in the manual CC group (55 ± 26 min vs. 22 ± 11 min, respectively; P < 0.05), and the survival-to-hospital discharge rates were 13% and 36%, respectively (see Table 3 in Reference 1). The prolonged low-flow time is notable because it may aggravate pulmonary ischemia–reperfusion injuries (2, 3) (e.g., edema, effusion, and consolidation).

Third, compared with the manual CC group, the mechanical CC group had a higher proportion of patients receiving venaorterial extracorporeal membrane oxygenation (v-a ECMO), which may have contributed to the higher incidence of lung edema. It is known that watershed, caused by a rise in left ventricular afterload and reduction in transpulmonary blood flow that results in abnormal opening of the aortic valve and increased pressure in the left ventricle and left atrium, is a common complication in patients receiving v-a ECMO and a contributing factor in pulmonary edema (4). The authors did not show the results of echocardiography and could not exclude the effect of v-a ECMO on pulmonary edema.

Fourth, the authors assumed that the increased rate of pulmonary edema in the mechanical CC group might have been due to a rise in hydrostatic pressure gradient, but such an assumption requires validation via echocardiography or invasive hemodynamic monitoring. The variation in right atrial pressure was higher during mechanical CC than during manual CC, but the relationship between right atrial pressure and pulmonary edema needs further evaluation.

Taken together, we write this letter asking Magliocca and her colleagues whether it is possible for them to report the actual presence of CRALE by recruiting patient groups with balanced baselines (especially with respect to severity of disease), expanding on the etiologies of CA, adding pre-CA lung CT scans, and evaluating systolic and diastolic function via pre- and post-CA echocardiography (5). Only under these circumstances can the authors make a precise diagnosis of CRALE. Moreover, we recommend analyzing the relationship between hydrostatic pulmonary edema and increased hydrostatic pressure gradient by using a Pulse index Continuous Cardiac Output device to monitor the global ejection fraction, extravascular lung water index, and pulmonary vascular permeability index.

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AUTHOR DISCLOSURES are available with the text of this letter at www.atsjournals.org.

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and
We read with interest the letter by He and colleagues suggesting that cardiopulmonary resuscitation (CPR)-associated lung edema (CRALE) (1) could be overestimated because of the possible presence of lung edema before cardiac arrest (CA). As a consequence, they recommend providing computed tomography (CT) and functional data before CA in our patients. Moreover, they reported the presence of CRALE in original data from patients with in-hospital CA (IHCA). The proportion of CRALE—evaluated with lung CT or X-ray before and after IHCA—decreased from 25% to 22% because 3% of patients had lung edema before CA.

First, it is basically impossible to have physiological data before CA in a population of patients with out-of-hospital CA (OHCA). Interestingly, the frequency of CRALE reported by He and colleagues in patients with IHCA is very similar (albeit slightly higher) compared with what we found in OHCA (22% vs. 17%). IHCA is a condition with distinct epidemiology and clinical course, compared with OHCA. Indeed, patients with IHCA show a higher proportion of comorbidities, witnessed arrest, and a shorter time to advanced life support with drugs administration (2). The majority of IHCA (54.6%) occurs in the ICU, operating room, or emergency department (2). Importantly, respiratory failure is a preexisting condition in 42% of patients with IHCA (34% of patients with IHCA being already invasively ventilated) (3). Moreover, He and colleagues diagnosed CRALE in some patients (whose percentage is not reported) relying on chest X-ray, whose interpretation is often subjective (4), whereas we relied on quantitative CT scan. Unfortunately, He and colleagues did not report the incidence of manual versus mechanical CC, as this would also represent an interesting aspect to compare. They suggested that “changes between pre- and post-CA radiological results might be more qualified as the indicator for diagnosing CRALE.” However, a

![Figure 1. Linear regression between levels of intrathoracic pressure—estimated by the measurement of pleural pressure using an esophageal balloon—and right atrial pressure in a pig undergoing 25-minute cardiopulmonary resuscitation of alternate phases of mechanical and manual CCs after cardiac arrest. Two-tailed P value = 0.005; Pearson’s correlation coefficient = +0.636; linear regression β coefficient = 0.621 (95% confidence interval, 0.312–0.929). The 95% confidence interval was adjusted by robust clustering for five clusters in time (i.e., five clusters of 5 min each during 25-min cardiopulmonary resuscitation). CC = chest compression.]

References
1. Magliocca A, Rezoagli E, Zani D, Manfredi M, De Giorgio D, Olivari D, et al. Cardiopulmonary Resuscitation-associated Lung Edema (CRALE). A translational study. Am J Respir Crit Care Med 2021;203:447–457.
2. Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: a review. JAMA 2019;321:1200–1210.
3. den Hengst WA, Gielis JF, Lin JY, Van Schil PE, Van Denplas P, et al. Lung ischemia-reperfusion injury: a molecular and clinical view on a complex pathophysiological process. Am J Physiol Heart Circ Physiol 2010;299:H1283–H1299.
4. Hoepel MM, Tudorache I, Kühl C, Marsch G, Hartung D, Wiesner O, et al. Extracorporeal membrane oxygenation: a translational study. Circulation 2014;130:864–865.
5. Price S, Platz E, Cullen L, Tavazzi G, Christ M, Cowie MR, et al.; Acute Heart Failure Study Group of the European Society of Cardiology Acute Cardiovascular Care Association. Expert consensus document: Echocardiography and lung ultrasonography for the assessment and management of acute heart failure. Nat Rev Cardiol 2017;14:427–440.

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Reply to He et al.

From the Authors:

We read with interest the letter by He and colleagues suggesting that cardiopulmonary resuscitation (CPR)-associated lung edema

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