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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 (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

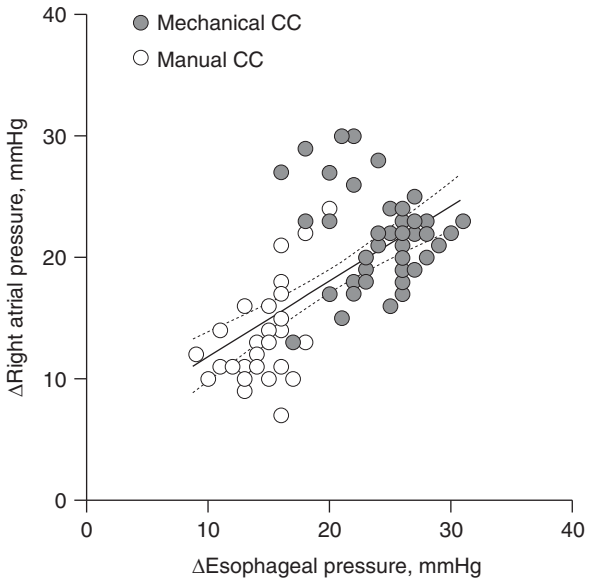

Figure 1. Linear regression between levels of intrathoracic pressure—estimated by the measurement of pleural pressure using an esophageal balloon—and right atrial pressure in a pig undergoing 25-minute cardiopulmonary resuscitation of alternate phases of mechanical and manual CCs after cardiac arrest. 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.

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Table 1. Etiology and Characteristics of Patients with OHCA with CRALE

Patient No.	Age (*yr*)	Sex	Comorbidities	CA Cause	First Monitored Rhythm	No-Flow Time (*min*)	Low-Flow Time (*min*)	Mechanical CC
1	70	M	Hypertension, dyslipidemia	Cardiac	VF	1	30	No
2	73	M	Hypertension	Cardiac	Asystolia	15	15	No
3	72	F	Hypertension, type 2 diabetes	Cardiac	PEA	0	23	No
4	43	M	None	Cardiac	VF	1	60	Yes
5	55	F	HIV, type 2 diabetes, smoking	Distributive shock due to bowel ischemia	PEA	1	95	Yes
6	54	M	Hypertension, dyslipidemia, smoking, alcohol abuse, peripheral arterial disease	Cardiac	VF	6	72	Yes
7	34	M	Hypertrophic cardiomyopathy	Cardiac	VF	4	85	Yes
8	74	F	Hypertension, history of tobacco use	Cardiac	Asystolia	2	47	Yes
9	41	M	Hypertension, sickle cell disease	Neurological catastrophe	PEA	0	38	Yes

Definition of abbreviations: CA = cardiac arrest; CC = chest compression; CRALE = cardiopulmonary resuscitation–associated lung edema; OHCA = out-of-hospital CA; PEA = pulseless electrical activity; VF = ventricular fibrillation.
Cardiac causes of cardiac arrest include acute coronary syndrome, arrhythmia from cardiomyopathy, and structural heart disease (6).

pre-CA lung CT is unfeasible in patients with OHCA, and it cannot be performed before starting CPR.

Second, we would like to point out that the purpose of our clinical investigation was not the validation of CRALE diagnosis. Contrarily, we tested the hypothesis that CPR could be associated with lung abnormalities and that mechanical and manual chest compression could have played a different role in developing lung injury. Based on the hypothesis-generating experimental study in a porcine model of CA and prolonged CPR, we aimed to explore the presence of CRALE in a preliminary retrospective clinical study. As He and colleagues point out, we cannot completely exclude the presence of preexisting pulmonary edema, but we applied specific exclusion criteria as per online supplemental material (1) to minimize this risk. Specifically, the presence of chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease, asthma, idiopathic pulmonary fibrosis, pulmonary hypertension, and cystic fibrosis) were exclusion criteria in our clinical investigation, and so were the presence of aspiration pneumonia, pulmonary embolism, lung cancer, and trauma. Unfortunately, in our manuscript, we did not report the cause of CA. However, acute respiratory failure was not the cause of CA in patients with CRALE, as reported in Table 1.

Third, He and colleagues suggested that low-flow time might worsen edema based on an ischemia–reperfusion mechanism. In our analyses, we reported that mechanical chest compression and a low-flow time >26 minutes both positively associate with the onset of CRALE. The combination of both factors may further contribute to the development of lung damage.

Fourth, regarding the lack of echocardiography to rule out the presence of watershed during venoarterial extracorporeal membrane oxygenation—defined as a "common phenomenon"—this is an interesting hypothesis but is based, to the best of our knowledge, only on a case report of a patient undergoing venoarterial extracorporeal membrane oxygenation after pulmonary embolism (i.e., one of our exclusion criteria). Anyhow, hemodynamic variables are reported in the online supplement for Reference 1.

Fifth, we reported data on right atrial pressure to estimate the higher intrathoracic pressure swings and negative pressure levels during mechanical chest compression that potentially cause CRALE. The authors advocate for echocardiography or invasive hemodynamic measurements to validate this hypothesis. Although echocardiography is hardly obtainable during CPR, we provided hemodynamic and echocardiographic variables at baseline and at 10, 120, and 180 minutes after resuscitation in a pig randomized to mechanical or manual chest compression during ambulance transport (*see* Table E2 in the online supplement for Reference 1) (5). As shown, no differences were detected in systolic, diastolic, and right atrial pressure; $\dot{Q}$; and left ventricular ejection fraction. As we are currently investigating the physiological mechanism behind the development of CRALE, we now provide data showing that intrathoracic pressure variation measured through an esophageal balloon tightly correlates with the right atrial pressure during both manual and mechanical chest compression in a porcine model of CPR (Figure 1; $r = 0.64$; $P = 0.005$).

Finally, we thank the authors for their suggestion to use transpulmonary thermodilution for the measurement of intra- and extravascular volumes. However, we do not see how this would inform us about the capillary pressure.

In conclusion, the key message we may derive from this vibrant correspondence is that irrespective of the in- or out-of-hospital setting of CA, CRALE occurs in both populations, although in IHCA this could be overestimated because of a preexisting lung disease. Thus, Dr. He's letter further corroborates our description of this novel phenomenon, which probably deserves greater attention. Indeed, future studies are needed to better understand the pathophysiology of CRALE and its eventual impact on CA outcome. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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