Cardiopulmonary Resuscitation–associated Lung Edema: The Price to Pay to Get the Heartbeat?

In this issue of the *Journal*, Magliocca and colleagues (pp. 447–457) reported the new concept of cardiopulmonary resuscitation (CPR)-associated lung edema (CRALE) in a translational study involving swine models and patients who suffered out-of-hospital cardiac arrest (1). Based on systematic computed tomography analysis in both animal experiments and clinical series, the authors accurately described for the first time the lung damages induced by chest compressions during CPR. Lung injury was observed in about one-third of cases, which is in line with the few previously published data in the field (2–4). This CRALE would be a new part of the postresuscitation disease that is nowadays recognized as a specific and complex entity (5). The novelty is that despite a strong rationale supporting the idea that successfully resuscitated patients with cardiac arrest may suffer from authentic lung injury, the concept of postresuscitation disease had been so far essentially considered from a hemodynamic perspective (6). CRALE will be from now on an additional piece of this complex puzzle that must be taken into account in the management of patients with cardiac arrest. These findings are of high clinical value, as some studies previously suggested that acute respiratory distress syndrome after cardiac arrest significantly affects ICU stay and chance of survival (2–4). According to their hypothesis, Magliocca and colleagues observed that this novel syndrome called "CRALE" was much more prone to occur during mechanical compared with manual CPR.

These observations reactivate the controversy regarding the clinical benefit of mechanical chest compressions and raise several questions concerning ventilation strategies during CPR.

Despite cumulating scientific literature, the superiority of mechanical over manual CPR is still a controversial issue (7–9). The clinical benefit in the daily practice, if any, appears modest, and the reasons explaining these results remain matters of debate. Although mechanical CPR does not improve survival in patients with out-of-hospital cardiac arrest, the CRALE could put the boot in by describing a new adverse event. Though Magliocca and colleagues had reported greater hemodynamic support and systemic perfusion generated by mechanical chest compressions compared with manual chest compressions during ambulance transport in a porcine model of CPR (10), the same group provides evidence in the present study that the severity of lung damage was greater in the mechanical chest compressions group. Then does mechanical CPR–related lung injury preclude us to observe the expected hemodynamic benefits? In other words, would the answer be in looking for new ways of improvement of ventilation strategies during and after CPR rather than giving up with this technique?

The accurate description of the mechanisms involved in CRALE reported in the *Journal* is indeed a promising opportunity to reconsider ventilation during CPR. In its pioneer work, Safar and colleagues reported V_T generated by chest compressions in intubated patients with cardiac arrest was too small to be measured, whereas similar chest compressions generated almost 150 ml in intubated healthy subjects (11, 12). This finding, though unfortunately neglected for years, was certainly the first observation of what was recently reported as "thoracic airway closure." During CPR, repetitive chest compressions result in a significant reduction in lung volumes below end-expiratory lung volumes that may favor small airways closure and affect gas exchange (13, 14). Interestingly, airway closure has been also recently reported in patients with acute respiratory distress syndrome (15). Thus, CRALE could be the clinical result of the dynamic reduction of lung volumes occurring during CPR. This could partly explain the greater impact of mechanical chest compressions. Interestingly, positive pressure may overcome airway closure and limit lung volume reduction. Whether a ventilation strategy based on moderate positive end-expiratory pressure (PEEP) level during CPR could be able to limit the occurrence of CRALE is an important question to address.

We already know that a systematic V_T reduction limits the occurrence of lung injury after cardiac arrest (2). Additional studies describing lung and chest wall mechanics as well as lung volumes and gas exchanges are needed to complete the description of CRALE to consider specific ventilation strategies in the particular settings of postresuscitation disease. Identifying patients at risk of CRALE is crucial to adapt ventilator settings at the early stage of this syndrome. This is even more important because caregivers are usually afraid to increase PEEP or put the patient prone in the context of postresuscitation care.

The important findings reported by Magliocca and colleagues as well as their previously published works highlight the imperative need to consider both hemodynamics and respiratory mechanics during and after CPR, revisiting heart–lung interactions in patients with cardiac arrest. ■

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

Guillaume Geri, M.D., Ph.D.
Medical Intensive Care Unit
Ambroise Paré Hospital, AP-HP
Boulogne Billancourt, France
Paris-Saclay University
Gif-sur-Yvette, France
and
INSERM UMR1018, CESP
Villejuif, France

Originally Published in Press as DOI: 10.1164/rccm.202009-3445ED on September 23, 2020

Jean-Christophe Richard, M.D., Ph.D.
Département de Médecine Intensive-Réanimation et Médecine Hyperbare
Université d'Angers
Angers, France
and
INSERM UMR 955 Eq13
Créteil, France

ORCID ID: 0000-0002-7691-6635 (G.G.).

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 Resp Crit Care Med* 2021;203:447–457.
2. Johnson NJ, Caldwell E, Carlbom DJ, Gaieski DF, Prekker ME, Rea TD, *et al*. The acute respiratory distress syndrome after out-of-hospital cardiac arrest: incidence, risk factors, and outcomes. *Resuscitation* 2019;135:37–44.
3. Kim JS, Kim YJ, Kim M, Ryoo SM, Sohn CH, Ahn S, *et al*. Impact of lung compliance on neurological outcome in patients with acute respiratory distress syndrome following out-of-hospital cardiac arrest. *J Clin Med* 2020;9:527.
4. Beitler JR, Ghafouri TB, Jinadasa SP, Mueller A, Hsu L, Anderson RJ, *et al*. Favorable neurocognitive outcome with low tidal volume ventilation after cardiac arrest. *Am J Respir Crit Care Med* 2017;195:1198–1206.
5. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, *et al*. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. *Circulation* 2002;106:562–568.
6. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, *et al*. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol* 2002;40:2110–2116.
7. Perkins GD, Lall R, Quinn T, Deakin CD, Cooke MW, Horton J, *et al*.; PARAMEDIC trial collaborators. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *Lancet* 2015;385: 947–955.
8. Hallstrom A, Rea TD, Sayre MR, Christenson J, Anton AR, Mosesso VN Jr, *et al*. Manual chest compression vs use of an automated chest compression device during resuscitation following out-of-hospital cardiac arrest: a randomized trial. *JAMA* 2006;295:2620–2628.
9. Rubertsson S, Lindgren E, Smekal D, Östlund O, Silfverstolpe J, Lichtveld RA, *et al*. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. *JAMA* 2014;311: 53–61.
10. Magliocca A, Olivari D, De Giorgio D, Zani D, Manfredi M, Boccardo A, *et al*. LUCAS versus manual chest compression during ambulance transport: a hemodynamic study in a porcine model of cardiac arrest. *J Am Heart Assoc* 2019;8:e011189.
11. Safar P, Brown TC, Holtey WJ, Wilder RJ. Ventilation and circulation with closed-chest cardiac massage in man. *JAMA* 1961;176:574–576.
12. Safar P, Brown TC, Holtey WJ. Failure of closed chest cardiac massage to produce pulmonary ventilation. *Dis Chest* 1962;41:1–8.
13. Cordioli RL, Lyazidi A, Rey N, Granier JM, Savary D, Brochard L, *et al*. Impact of ventilation strategies during chest compression: an experimental study with clinical observations. *J Appl Physiol (1985)* 2016;120:196–203.
14. Chen L, Del Sorbo L, Grieco DL, Junhasavasdikul D, Rittayamai N, Soliman I, *et al*. Potential for lung recruitment estimated by the recruitment-to-inflation ratio in acute respiratory distress syndrome: a clinical trial. *Am J Respir Crit Care Med* 2020;201:178–187.
15. Grieco DL, J Brochard L, Drouet A, Telias I, Delisle S, Bronchti G, *et al*. Intrathoracic airway closure impacts CO_2 signal and delivered ventilation during cardiopulmonary resuscitation. *Am J Respir Crit Care Med* 2019;199:728–737.

One Molecule, Two Opposite Biological Effects: The Many Faces of Matrix Metalloproteases in the Pathogenesis of Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease of unknown etiology and limited therapeutic options that remains a leading cause of death among those with interstitial lung diseases. Thus, it is characterized by the unrelenting accumulation of scar tissue, resulting in the destruction of lung architecture and the progressive decline of lung function (1).

The pathogenesis is uncertain, but strong evidence indicates that the aberrant activation of airways and alveolar epithelial cells initiates the development of the disease through the secretion of numerous mediators, including several MMPs (matrix metalloproteinases) (1–3).

MMPs are a family of zinc-dependent matrixins that participate in extracellular matrix degradation but also process and cleave diverse bioactive mediators, such as growth factors, cytokines, and chemokines, playing a critical role in a wide variety of biological and pathological processes (4). From these, a growing body of evidence has demonstrated that MMP-9 is elevated in IPF lungs being expressed by different types of lung cells (4, 5). Outstandingly, this enzyme has a bidirectional relationship with TGF-β1, likely the strongest profibrotic mediator. Thus, Thy-1$^-$ fibroblasts, which are usually located in the fibroblast/myofibroblast foci, stimulated by lung epithelium-produced TGF-β1 synthesize MMP-9, and MMP-9 activates latent TGF-β1, contributing to the increase in the pool of active TGF-β1 (4–7).

In this issue of the *Journal*, Espindola and colleagues (pp. 458–470) evaluated the expression of MMP-9 in IPF airway basal-like cells and the effects of MMP-9 inhibition on fibrotic mechanisms with the hypothesis that targeting this enzyme would attenuate the fibrotic response (8).

First, the investigators aimed to identify the cells expressing MMP-9 in IPF and normal lungs and found a marked increase in

Originally Published in Press as DOI: 10.1164/rccm.202008-3330ED on October 22, 2020