Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation* 2008;118:2452–2483.
2. Gladwin MT, Kanias T, Kim-Shapiro DB. Hemolysis and cell-free hemoglobin drive an intrinsic mechanism for human disease. *J Clin Invest* 2012;122:1205–1208.
3. Lehle K, Lubnow M, Philipp A, Foltan M, Zeman F, Zausig Y, *et al*. Prevalence of hemolysis and metabolic acidosis in patients with circulatory failure supported with extracorporeal life support: a marker for survival? *Eur J Heart Fail* 2017;19:110–116.
4. Lei C, Berra L, Rezoagli E, Yu B, Dong H, Yu S, *et al*. Nitric oxide decreases acute kidney injury and stage 3 chronic kidney disease after cardiac surgery. *Am J Respir Crit Care Med* 2018;198: 1279–1287.
5. Minneci PC, Deans KJ, Zhi H, Yuen PS, Star RA, Banks SM, *et al*. Hemolysis-associated endothelial dysfunction mediated by accelerated NO inactivation by decompartmentalized oxyhemoglobin. *J Clin Invest* 2005;115:3409–3417.
6. Minamishima S, Kida K, Tokuda K, Wang H, Sips PY, Kosugi S, *et al*. Inhaled nitric oxide improves outcomes after successful cardiopulmonary resuscitation in mice. *Circulation* 2011;124: 1645–1653.
7. Derwall M, Ebeling A, Nolte KW, Weis J, Rossaint R, Ichinose F, *et al*. Inhaled nitric oxide improves transpulmonary blood flow and clinical outcomes after prolonged cardiac arrest: a large animal study. *Crit Care* 2015;19:328.
8. Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon RO III, Schechter AN, *et al*. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. *Nat Med* 2002;8:1383–1389.
9. Yu B, Raher MJ, Volpato GP, Bloch KD, Ichinose F, Zapol WM. Inhaled nitric oxide enables artificial blood transfusion without hypertension. *Circulation* 2008;117:1982–1990.
10. Hayashida K, Bagchi A, Miyazaki Y, Hirai S, Seth D, Silverman MG, *et al*. Improvement in outcomes after cardiac arrest and resuscitation by inhibition of S-nitrosoglutathione reductase. *Circulation* 2019;139: 815–827.

CO_2 Oscillation during Cardiopulmonary Resuscitation: The Role of Respiratory System Compliance

To the Editor:

We read with interest the manuscript by Grieco and colleagues entitled "Intrathoracic Airway Closure Impacts CO_2 Signal and Delivered Ventilation During Cardiopulmonary Resuscitation" (1).

The authors conducted a very elegant clinical investigation corroborated by focused experiments in the Thiel cadaver model, describing a peculiar oscillatory capnographic pattern during cardiopulmonary resuscitation (CPR). From the results, it has been speculated that a low oscillating CO_2 during chest compressions is a result of the presence of airway collapse, which obstructs the airflow. However, as mentioned by the authors in the discussion, individual differences in the compliance of the respiratory system (Cpl,rs, including the lungs and the chest wall) could have a great prominence in explaining this finding. For a given pressure applied to the sternum during a chest compression, the gas volume displacement will be directly proportional to the compliance of the respiratory system. Therefore, patients with a lower airway opening index (AOI) may have had lower Cpl,rs. This would also explain the correlation between alveolar ventilation and AOI, because greater ventilation was likely in patients with higher compliance. Interestingly, a greater AOI was observed in patients with a shockable rhythm, who are likely to have a shorter duration of cardiac arrest compared with those with nonshockable rhythms and thus a lesser deterioration in Cpl,rs (2).

We wonder about the correlation between Cpl,rs measured during regular tidal ventilation and AOI.

Although small airway closure might affect the measurement of compliance, this is unlikely during regular tidal ventilation. We accept that a formal "static" measurement of Cpl cannot be obtained during chest compression, but a good estimate would be possible from the delivered V_T, given that a constant inspiratory pressure was applied. Indeed, a reliable value for Cpl,rs can be obtained in the Thiel cadavers.

Respiratory system compliance could also explain the beneficial effects of positive end-expiratory pressure (PEEP). Ventilation resulting from chest compression occurs between FRC and residual volume (3). At this level of lung volume, the pressure–volume curve of normal subjects is less compliant than it is above FRC (4). The application of PEEP would increase the end-expiratory lung volume and cause the chest compressions to "ventilate" the respiratory system in a more compliant part of the pressure–volume curve, leading to greater V_T and greater alveolar ventilation.

Finally, the "circulatory" component of CPR, that is, forward blood flow generated by chest compression, affects end-tidal CO_2 and might potentially affect the subsequent AOI calculation. Indeed, ventilation and hemodynamics are deeply interconnected in the pathophysiology of CPR, as $\dot{Q}$ is the major determinant of CO_2 transport to the lungs. Because $\dot{Q}$ may vary during CPR in relationship to chest compression quality and/or patient's condition, for example, development of stoned heart for prolonged resuscitation and Cpl,rs modification, the evolving AOI may change over time.

In conclusion, although we believe that the work by Grieco and colleagues does not completely tease out the relative contributions of compliance versus airway closure in the generation of CO_2 oscillation, their findings have tremendous clinical relevance, particularly for the potential benefits of PEEP during CPR, and highlight the importance of more studies on the topic. ■

Originally Published in Press as DOI: 10.1164/rccm.201812-2331LE on January 25, 2019

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

Emanuele Rezoagli, M.D.
University of Milan-Bicocca
Monza, Italy

Aurora Magliocca, M.D.
University of Milan-Bicocca
Monza, Italy
and
Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Milan, Italy

Giuseppe Ristagno, M.D., Ph.D.
Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Milan, Italy

Giacomo Bellani, M.D., Ph.D.*
University of Milan-Bicocca
Monza, Italy
and
San Gerardo Hospital
Monza, Italy

ORCID IDs: 0000-0002-4506-7212 (E.R.); 0000-0002-3089-205X (G.B.).

*Corresponding author (e-mail: giacomo.bellani1@unimib.it).

References

1. Grieco DL, Brochard L, Drouet A, Telias I, Delisle S, Bronchti G, *et al*.; CAVIAR Group. Intrathoracic airway closure impacts CO_2 signal and delivered ventilation during cardiopulmonary resuscitation. *Am J Respir Crit Care Med* [online ahead of print] 26 Sep 2018; DOI: 10.1164/rccm.201806-1111OC.
2. Davis K Jr, Johannigman JA, Johnson RC Jr, Branson RD. Lung compliance following cardiac arrest. *Acad Emerg Med* 1995;2: 874–878.
3. Idris AH, Banner MJ, Wenzel V, Fuerst RS, Becker LB, Melker RJ. Ventilation caused by external chest compression is unable to sustain effective gas exchange during CPR: a comparison with mechanical ventilation. *Resuscitation* 1994;28:143–150.
4. West JB. Respiratory physiology: the essentials. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.

Reply to Rezoagli *et al.*

From the Authors:

We read with great interest the letter by Rezoagli and colleagues, and we are grateful to the authors for opening a constructive discussion on the intrathoracic airway closure phenomenon that we recently reported in a relevant proportion of patients receiving cardiopulmonary resuscitation (CPR) (1). Rezoagli and coworkers suggest that the nonoscillating, steady capnogram reported in patients and cadavers may be in part explained by the drop in respiratory system compliance caused by cardiac arrest and CPR-induced lung volume loss. As a consequence, they hypothesized that the low airway opening index detected in some patients (nonoscillating or poorly oscillating capnogram) reflects the absence of fresh gas flow entering the system, and may be caused by the scarce volume displacement produced by chest compressions at a constant pressure in case of low compliance, rather than airway closure. Indeed, we previously reported that chest compressions induce huge lung volume loss (2), which can result in a reduction in respiratory system compliance (3, 4).

We think that several points support the major role played by airway closure/patency to explain our findings. First, the volume generated by chest compressions was measured as the volume entering the system during chest decompression. A careful examination of the tracings that we reported in patients (5), lung model, and cadavers (1, 2) shows that the flow is limited ("capped") or absent during decompression. A limitation of flow (6) secondary to airway closure during CPR can occur during decompression because of a dynamic drop in the transmural pressure of the airways. In case of airway patency, the driving force of the flow during chest decompression is the respiratory system recoil force, which lowers alveolar pressure, generating a pressure gradient throughout the airways. In case of airway closure, the alveolar pressure is no longer transmitted to the airway opening, thereby hampering any inspiratory flow. Interestingly, in case of low compliance, this recoil pressure could potentially be higher.

Second, Rezoagli and coworkers suggest that, "For a given pressure applied to the sternum during a chest compression, the gas volume displacement is directly proportional to the compliance of the respiratory system." This could have been true in the patients undergoing manual CPR. Although guidelines suggest to maintain chest compression depth within a range (7), rescuers may perform CPR with a constant pressure, yielding variable volume displacement according to different compliance. In the experiments conducted in human cadavers and on a bench model, we used a mechanical device (LUCAS 2; Jolife AB/Physio-Control), which is a piston that provides constant chest compression depth, independent from the pressure needed to achieve it. Thus, all the cadavers likely received the same ventral-to-dorsal displacement, which resulted in different changes in intrathoracic/alveolar pressure according to respiratory system and lung compliance; accordingly, we provide a figure showing that the change in the intrathoracic pressure resulting from chest compressions (i.e., a dependent variable if the LUCAS is used) was variable in the three cadavers we studied (Figure 1, left). There was no correlation between the changes in airway opening index and the intrathoracic pressure change resulting from chest compression (Figure 1, right). Moreover, in an exploratory analysis [Supplementary Table 2 in the manuscript (1)], we tested whether airway opening index was affected by whether chest compressions were performed manually or with a mechanical device (constant ventral-to-dorsal displacement, variable applied pressure); there was no difference in our cohort.

Third, the ventilatory mode used in our cohort of patients and in experimental settings was pressure-regulated and maintained some positive pressure at end-expiration. This could result in low V_T insufflation as compliance diminishes (8), as suggested by the authors. Nevertheless, because of the continuous chest compression strategy, two or three compressions/decompressions occur during the 1-second high-pressure time of cardiopulmonary ventilation mode. The huge positive pressure generated by chest compression (reducing transpulmonary

Originally Published in Press as DOI: 10.1164/rccm.201901-0044LE on January 25, 2019