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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

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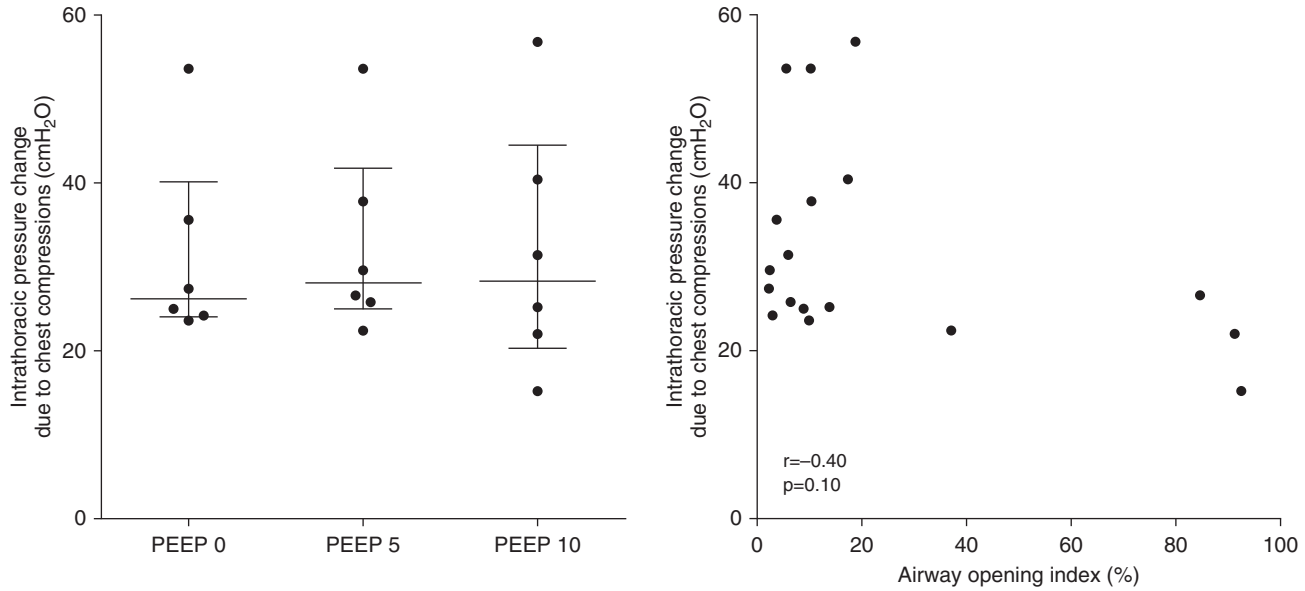

Figure 1. Three cadavers were studied during chest compressions and pressure-regulated ventilation at a rate of 10/min at three different positive end-expiratory pressure (PEEP) levels (0, 5, and 10 cm H_2O) in a sequential order for 5 minutes: each cadaver was studied twice while administering 5% and 10% CO_2, yielding 18 individual observations (2). (Left) Individual values of the intrathoracic pressure change produced by chest compressions in the three studied cadavers at three PEEP levels. Medians and interquartile ranges are displayed. (Right) Lack of relationship between the changes in the intrathoracic pressure (estimated by esophageal pressure) resulting from chest compressions and airway opening index. Because the ventral-to-dorsal displacement of the thorax caused by the mechanical device was constant, the intrathoracic pressure change resulting from chest compressions reflects system elastance (and compliance).

pressure) is expected to markedly reduce insufflated volume, almost irrespective of the compliance. Conversely, inspired V_T mostly depends on the volume driven by chest decompressions occurring at high airway pressure, which again depends on the recoil pressure expected to be limited by airway closure.

Finally, the fact that we used a mode maintaining positive pressure at end expiration reduced the incidence of airway closure. Without any expiratory positive pressure, we would have seen many more patients having no transmission of chest compression on airway pressure, reinforcing the independence from compliance.

On the whole, the hypothesis that low compliance may in part explain low-oscillating, steady capnograms appears unlikely because of the preeminent role of chest decompression in this context, whose efficiency in driving ventilation appears to critically depend on patency/closure of the airways. ■

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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. Charbonney E, Delisle S, Savary D, Bronchti G, Rigollot M, Drouet A, *et al*.; CAVIAR. A new physiological model for studying the effect of chest compression and ventilation during cardiopulmonary resuscitation: the Thiel cadaver. *Resuscitation* 2018;125: 135–142.
3. Grieco DL, Russo A, Romanò B, Anzellotti GM, Ciocchetti P, Torrini F, *et al*. Lung volumes, respiratory mechanics and dynamic strain during general anaesthesia. *Br J Anaesth* 2018;121: 1156–1165.
4. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure: computed tomographic scan study. *Am Rev Respir Dis* 1987;136: 730–736.
5. Cordioli RL, Lyazidi A, Rey N, Granier J-M, 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.
6. Junhasavasdikul D, Telias I, Grieco DL, Chen L, Gutierrez CM, Piraino T, *et al*. Expiratory flow limitation during mechanical ventilation. *Chest* 2018;154:948–962.
7. Soar J, Nolan JP, Böttiger BW, Perkins GD, Lott C, Carli P, *et al*.; Adult advanced life support section Collaborators. European

Resuscitation Council Guidelines for Resuscitation 2015: section 3: adult advanced life support. *Resuscitation* 2015;95: 100–147.
8. Rittayamai N, Katsios CM, Beloncle F, Friedrich JO, Mancebo J, Brochard L. Pressure-controlled vs volume-controlled ventilation in acute respiratory failure: a physiology-based narrative and systematic review. *Chest* 2015;148:340–355.

Preserved Ratio Impaired Spirometry and Interstitial Lung Abnormalities in Smokers

To the Editor:

I read with great interest the paper by Wan and coworkers evaluating the preserved ratio impaired spirometry (PRISm) functional pattern ($FEV_1/FVC \geq 0.7$ and $FEV_1 > 80\%$) in their longitudinal study of a large cohort of current or ex-smokers (1). The prevalence of this heterogeneous condition is remarkable (12.4% and 12.5% at baseline and follow-up, respectively) and its association with increased mortality, comparable to that observed in Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2 subjects, deserves special consideration. Individuals with PRISm are characterized by a significantly lower TLC% predicted and percent emphysema, as measured on quantitative computed tomography scans, in comparison with GOLD 0 and GOLD 1–4 groups.

In the study cohort, the PRISm status was not stable at 5-year follow-up; in particular, the authors report a transition to GOLD 0 in 22% of the subjects with PRISm and a transition to PRISm in about one-third of baseline GOLD 0 individuals. The latter group was characterized by a lesser amount of emphysema and air trapping on computed tomography scans, an increase in body mass index, and decreased TLC% predicted and percent emphysema at baseline. Moreover, this group exhibited the largest functional decline (either FEV_1 or FVC) in comparison with all other groups, suggesting a restrictive physiologic impairment.

Interstitial lung abnormalities have been found in a substantial minority of a cohort of smokers enrolled in the COPDGene (Genetic Epidemiology of Chronic Obstructive Pulmonary Disease) study (1 out of 12) and were associated with a reduced TLC and a lesser amount of emphysema. Smokers with interstitial lung abnormalities were more likely to have an "unclassified" spirometric pattern, analogous to PRISm (2). Under this definition are grouped various morphological pictures that may represent static imaging findings or the early stage of a progressive fibrosing disease (3).

The evidence of many similarities between smokers identified as carriers of interstitial lung abnormalities and those functionally classified as having PRISm makes me think that at least a small subset of baseline GOLD 0 subjects who transitioned to the PRISm group could have developed a smoke-related interstitial disorder. ■

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References

1. Wan ES, Fortis S, Regan EA, Hokanson J, Han MK, Casaburi R, *et al.*; COPDGene Investigators. Longitudinal phenotypes and mortality in preserved ratio impaired spirometry in the COPDGene Study. *Am J Respir Crit Care Med* 2018;198:1397–1405.
2. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, *et al*. COPDGene investigators: lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med* 2011;364:897–906.
3. Araki T, Putman RK, Hatabu H, Gao W, Dupuis J, Latourelle JC, *et al*. Development and progression of interstitial lung abnormalities in the Framingham Heart Study. *Am J Respir Crit Care Med* 2016;194: 1514–1522.

Reply to Marruchella

From the Authors:

On behalf of our coauthors, we thank Dr. Marruchella for his interest in the longitudinal analysis of Preserved Ratio Impaired Spirometry (PRISm) ($FEV_1/FVC \geq 0.7$ and $FEV_1 < 80\%$ predicted) in the COPDGene (Genetic Epidemiology of Chronic Obstructive Pulmonary Disease) study (1) and for bringing attention to the possible role of interstitial lung abnormalities in PRISm. Among the first 2,500 subjects enrolled in phase 1 of the COPDGene study, a significantly higher prevalence of interstitial lung abnormalities on chest computed tomography imaging was noted among the PRISm subgroup, then referred to by the moniker "GOLD-Unclassified," relative to the remainder of the COPDGene cohort (22% vs. 10–13% among GOLD 0–4) (2). This same research group subsequently extended their visual assessment

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