Ventilation Is an Important Confounding Variable When End-Tidal Carbon Dioxide Is Used to Help Guide Cardiopulmonary Resuscitation

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GLOSSARY

AHA = American Heart Association; **CI** = confidence interval; **CO_2** = carbon dioxide; **CPR** = cardiopulmonary resuscitation; **$Etco_2$** = end-tidal carbon dioxide; **PEEP** = positive end-expiratory pressure; **ROSC** = return of spontaneous circulation

The American Heart Association (AHA) further refined cardiopulmonary resuscitation (CPR) in the 2015 AHA CPR and emergency cardiac care guidelines by recognizing end-tidal carbon dioxide ($Etco_2$) as an important adjuvant for prognosticating the outcome of CPR.[1] The 2015 guidelines state: "In intubated patients, failure to achieve an $Etco_2$ of greater than 10 mm Hg by waveform capnography after 20 [min] of CPR may be considered as one component of a multimodal approach to decide when to end resuscitation efforts, but should not be used in isolation."[1] We applaud the recommendation but caution about strict $Etco_2$ interpretation in the setting of CPR.

RATIONALE FOR MEASURING $ETCO_2$ DURING CPR

Resuscitation measures are aimed at maximizing perfusion to the heart and brain.[2,3] Even at its best, CPR creates very subphysiological cardiac output. Because direct measurements of cardiac output during CPR are not available, other measurements including arterial blood pressure, central venous oxygen saturation, and quantitative waveform capnography have been advanced as clinical surrogates of cardiac output.[4,5] They can serve as sensitive indicators of return of spontaneous circulation (ROSC) and can be monitored continuously without interrupting CPR.[1]

Clinical studies show a direct relationship between $Etco_2$ values and cardiac output produced by chest compressions.[6,7] Mean $Etco_2$ levels <3 mm Hg immediately after cardiac arrest increase to >7 mm Hg with initiation of chest compressions. Mean $Etco_2$ spikes to >28 mm Hg within 30 seconds of ROSC. A sudden increase in $Etco_2$ (absent an injection of sodium bicarbonate) is typically the earliest clinical indicator of ROSC.[8,9] This often occurs before the return of a palpable pulse. A rise in $Etco_2$ by ≥10 mm Hg has an 83% (95% confidence interval [CI], 62%–95%) positive predictive value for ROSC.[10] Based on these findings, monitoring $Etco_2$ virtually eliminates the need to stop chest compressions to check for pulses. Several unblinded, design-limited, observational studies have reported that an $Etco_2$ ≤10 mm Hg could accurately predict a nonsurvivable injury in patients receiving appropriate CPR.[11,12] One recurring major study limitation is the unmeasured minute ventilation during CPR.

PHYSIOLOGY OF $ETCO_2$ DURING CPR

The $Etco_2$ is the consequence of carbon dioxide (CO_2) production, transport, and elimination. When 2 of these determinants of $Etco_2$ are held constant, a change in $Etco_2$ reflects a change in the third. During an isolated perfusion problem, as evident during CPR with a fixed minute ventilation, pulmonary blood flow becomes the determinant of alveolar CO_2 delivery and thus $Etco_2$. Assuming normal gas exchange, pulmonary blood flow serves as a proxy for cardiac output. A low $Etco_2$ level reflects a low cardiac output if other variables are fixed and normal. These variables are often not fixed, and a low $Etco_2$ can also be a reflection of an airway leak, hyperventilation, pulmonary embolus, hypotension, and cardiac arrest.

Animal and human studies demonstrate a linear relationship between $Etco_2$ and cardiac output. One study showed that, in abdominal aortic aneurysm repair patients with constant minute ventilation, a linear relationship exists between percent changes in $Etco_2$ and percent changes in cardiac output.[13] This linear relationship holds true within a wide range of cardiac outputs, including values <25% of normal, which are in the range expected during human CPR. The direct relationship between $Etco_2$ and cardiac output in low-flow states requires a constant minute ventilation.[14]

During states of low blood flow, alterations in minute ventilation will significantly influence $Etco_2$ values just like changes in cardiac output will. In a multicenter cohort study of 583

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cardiac arrests, $Etco_2$ was lowered by an average of 3.0 mm Hg ($P < .001$) for every 10 breaths/min increase in ventilation rate.[15] A report of anesthetized patients observed relatively small changes in minute volume correlate with large changes in $Etco_2$.[16] As the cardiac output was not fixed or quantified in the human studies, a linear relationship between $Etco_2$ and minute ventilation has not been definitively established; however, it is clear that the $Etco_2$ value is sensitive to changes in minute ventilation during states of low cardiac output.

Despite the attractiveness of capnography, there are limitations during CPR because $Etco_2$ becomes difficult to interpret with dynamically changing ventilation and circulation. As an example, hypoventilation will elevate the $Etco_2$, but a simultaneous decrease in cardiac output will decrease pulmonary perfusion, and thus bidirectional changes can result in an unchanged $Etco_2$. Even in the ideal scenario with a patient experiencing an isolated circulatory problem, minute ventilation is difficult to precisely control without using a mechanical ventilator. Currently, manual ventilation is most commonly used during CPR despite high inter- and intraprovider variability with manual ventilation.[17] Most studies only describe respiratory rate because CPR providers generally do not use spirometry. Unsynchronized chest compressions add another level of variability and uncertainty to the delivery of ventilation.

DISCUSSION

The 2015 AHA CPR and emergency cardiac care guideline recognizing $Etco_2$ as an important adjuvant for prognosticating the outcome of CPR is identified as "weak" based on limited quality and quantity of data.[1] Furthermore, the guidelines offer a "weak" recommendation on respiratory rate that only applies to patients with an advanced airway: "After placement of an advanced airway, it may be reasonable for the provider to deliver [one] breath every 6 s (10 breaths/min) while continuous chest compressions are being performed."[1]

Perhaps one of the strongest arguments for monitoring minute ventilation during CPR is to prevent hyperventilation. Hyperventilation has been associated with worse survival rates and resuscitation outcomes in the setting of CPR.[18,19] Despite awareness of the detrimental effects of hyperventilation and the recommendation to ventilate 10 breaths/min, inappropriately high respiratory rates (>25 breaths/min) are very common during CPR.[1] Manual respiratory rate during CPR on intubated patients is more than double the recommended with a median of 21 breaths/min.[18] In contrast to data on the respiratory rate effect, there are limited data on the effects of tidal volume during CPR. One should also consider the potential for this unintended manual hyperventilation to prevent adequate time for breath egress and thereby create an auto positive end-expiratory pressure (autoPEEP) phenomenon through breath stacking. The autoPEEP subsequently increases intrathoracic pressure and limits the return of preload, leading to a hypotensive state manifested not only in a decrease in blood pressure but also in a confounding decrease in $Etco_2$. Thus, inadvertent manual hyperventilation can confound the interpretation of a low $Etco_2$ during CPR via either overventilating alone or overinflating the respiratory system and thereby decreasing pulmonary blood flow.

The effects of uncontrolled manual ventilation in comparison with controlled mechanical ventilation on $Etco_2$ values during CPR were examined in a meta-analysis.[2] The analysis found that participants receiving mechanical ventilation had on average 9.42 mm Hg higher (95% CI, 4.45–14.39) $Etco_2$ levels than those receiving manual ventilation, which is by itself a large enough $Etco_2$ to alter a survivability assessment (Figure).[2,18] A confounding consideration then becomes a potentially higher $Etco_2$ value associated with failure to effect ROSC when CPR is done under conditions of mechanical ventilation.

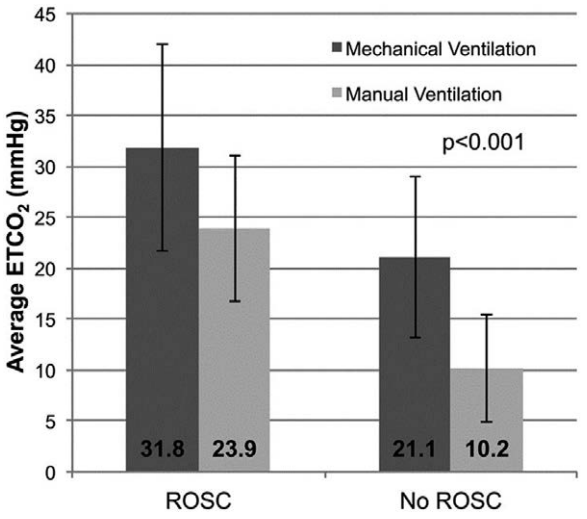

Figure. Comparison of mean $Etco_2$ values among patients in cardiac arrest who received mechanical versus manual ventilation. $Etco_2$ indicates end-tidal carbon dioxide; ROSC, return of spontaneous circulation. Hartmann SM, Farris RW, Di Gennaro JL, Roberts JS, *Journal of Intensive Care Medicine*, vol. 30, issue 7, pp. 426–435, copyright © 2015 by The Authors. Reprinted by Permission of SAGE Publications, Inc.[2]

CONCLUSIONS

Capnography is a valuable tool during CPR for confirming endotracheal tube placement and detecting ROSC, and it can provide information about the quality of CPR.[1] However, when ventilation and circulation are inconstant as during CPR, it becomes difficult to determine the contribution of each to the observed $Etco_2$ level and reach reliable conclusions about the quality of CPR.[2,9] Absent conditions of a steady minute ventilation $Etco_2$, interpretations during CPR should be made with caution because the AHA guidelines and clinical evidence leave unanswered questions. If the decision to terminate CPR includes not having achieved an $Etco_2$ of 10 mm Hg (under conditions of manual ventilation), one must also consider if the failure to achieve at least the 10 mm Hg target $Etco_2$ might be as much, or more, of a reflection of hyperventilation than low pulmonary blood flow/cardiac output.[20]

DISCLOSURES

Name: Maria Leinonen, MD.
Contribution: This author helped research, write, and edit the manuscript.
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Contribution: This author helped research, write, and edit the manuscript.
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