

WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**Worksheet author(s)**

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Clinical question.

In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does the use of a specific ventilation strategy (including specific CO2 goal) (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? **INTERVENTION**

State if this is a proposed new topic or revision of existing worksheet: **NEW TOPIC**

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? **No**

Search strategy (including electronic databases searched).

SEARCH UPDATED SEPTEMBER 29, 2009;

PubMed (1950-2009)

#1	Search post-resuscitation	411
#2	Search ventilation	207835
#3	Search post-resuscitation AND ventilation	56
#4	Search heart arrest	36807
#5	Search acid-base	23735
#6	Search acid-base heart arrest	239

<EXAMINED RESULTS OF #3 AND #6 FOR RELEVANT ARTICLES>

Ovid

Database: Ovid MEDLINE(R) <1950 to September Week 2 2008>

Search Strategy:

#1	heart arrest.mp. or Heart Arrest/	(24228)
#2	Ventilation/	(4039)
#3	1 and 2	(0)
#4	Carbon Dioxide/ or co2.mp.	(86641)
#5	4 and 1	(502)
#6	5 and "Humans".sa_suba.	(245)

<EXAMINED RESULTS OF #6 FOR RELEVANT ARTICLES>

EMBASE

#1 ('resuscitation'/exp OR 'resuscitation') AND ('co2'/exp OR 'co2') AND [humans]/lim(409)

SEPARATE SEARCH TO LOOK FOR ACUTE LUNG INJURY:**PubMed**

("ventilators, mechanical"[MeSH Terms] OR ("ventilators"[All Fields] AND "mechanical"[All Fields]) OR "mechanical ventilators"[All Fields] OR "ventilator"[All Fields]) AND ("lung injury"[MeSH Terms] OR "lung"[All Fields] AND "injury"[All Fields]) OR "lung injury"[All Fields]) AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields]) OR ("cardiac"[All Fields] AND "arrest"[All Fields]) OR "cardiac arrest"[All Fields]

9

Results

Hand searched reference lists of relevant articles to yield one additional clinical study, and three animal studies

- State inclusion and exclusion criteria

1. Included studies in humans

2. Included studies with measurement or control of ventilation strategy

3. Excluded studies of ventilation during CPR (THIS IS MAJORITY OF LITERATURE)

- Number of articles/sources meeting criteria for further review:

10 studies in humans were identified, but 4 were excluded on detailed review, leaving 6 studies in humans for evidence (3=LOE2; 2=LOE3; 1=LOE4)

In order to deepen the discussion, the restriction to human studies was relaxed, and animal studies that compared ventilation, hypercapnia or hypocapnia were also included:

10 studies in animals (10=LOE5)

Summary of evidence Evidence Supporting Clinical Question

Good		Buunk 1997, 1569 – E Esteban 2002, 345 - C	Wongsurakiat 2004, 1281 – C,E		<i>Ferakova 1995, 207 – E</i> <i>Vanicky 1992, 167 - E</i>
Fair					<i>Kagstrom 1983, 281 - E</i> <i>Kreps 2000, 2866 - E</i> <i>Kreps 2000, 2873 –E</i> <i>Schmitz 1997, 1202 - E</i>
Poor		Suljaga-Bechtel, 1984, 77 - C	Sunde 2007, 29 - D		<i>Ebmeyer 1994, S20 – E</i> <i>Safar 1996, 105 - D</i>
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event

C = Survival to hospital discharge
D = Intact neurological survival

E = Other endpoint
Italics = Animal studies

Evidence Neutral to Clinical Question

Good				Moon 2007, 219 - C	
Fair					
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event

C = Survival to hospital discharge
D = Intact neurological survival

E = Other endpoint
Italics = Animal studies

Evidence Opposing Clinical Question

Good					
Fair					<i>Hossman 1973, 271 – E</i> <i>Nemoto 1975, 425- E</i> <i>Todd 1985, 720 - E</i>
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event

C = Survival to hospital discharge
D = Intact neurological survival

E = Other endpoint
Italics = Animal studies

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Two effects of ventilation strategy are likely to affect outcome. First, the choice of ventilation pressures and volumes may be related to outcomes from acute lung injury (ALI). Various ALI-directed ventilation strategies have been developed, with most recent attention on low-volume/high-rate ventilation. While post-cardiac arrest patients are at risk of ALI, and many demonstrate pulmonary profiles consistent with ALI, lung-failure is not a common mode of death after cardiac arrest. Therefore, it is not surprising that there are few reports about the effects of ALI-oriented treatments on outcome after cardiac arrest.

Second, ventilation strategy effects on pCO₂ can alter cerebral blood flow. Cerebral blood flow remains CO₂-reactive after cardiac arrest, and hyperventilation has been demonstrated to reduce brain blood flow. Therefore, avoiding hyperventilation is a reasonable step for preventing additional ischemia to the recovering brain. The available literature seems to confirm and quantify the CO₂-responsiveness of the brain after cardiac arrest, but there are no real studies that intentionally manipulate ventilation to affect outcome. Instead, it appears that all investigators who have addressed ventilation took great care to target eucapnia for their subjects.

The review suggests the following conclusions: (1) There are minimal data to support or refute the benefit of an ALI-oriented ventilation strategy for patients after cardiac arrest. What data are available do not indicate profoundly beneficial or harmful effects. (2) Physiological data in humans suggest that hyperventilation could cause additional cerebral ischemia in the post-cardiac arrest patient. However, there are no prospective data to support or refute whether a strategy for avoiding hyperventilation-induced ischemia is independently beneficial.

SPECIFIC PAPERS:**CLINICAL STUDIES:**

Buunk 1997, 1569 performed an experimental study using transcranial Doppler of the middle cerebral artery in 10 comatose subjects. Hypoventilation (ie, hypercapnia) caused a significant increase in median flow velocity (MFV), a decrease in pulsatility index (PI), and an increase in jugular bulb PO₂ and SO₂. Hyperventilation (ie, hypocapnia) did not change the MFV and PI of the MCA, but decreased P_{jb}O₂ and S_{jb}O₂. Hyperventilation can decrease S_{jb}O₂ below the ischemic threshold (55%). These results suggested that hyperventilation should be avoided in order to avoid ischemia in post-cardiac arrest patients. However, ventilation was not sustained at a given level and related to long-term outcomes. (LOE2)

Esteban 2002, 345 looked prospectively at 28 day mortality in a cohort of 15757 ventilated patients that included a subset of 100 subjects with ventilation as a consequence of cardiac arrest. While cardiac arrest and coma had independent associations with mortality, there were also independent effects of high peak (>50 mmHg) and plateau pressures (>35 mmHg). Tidal volume and PEEP did not have independent effects in the multivariable model. (LOE2)

Moon 2007, 219 compared calculated shunts and CO₂ gradients between survivors and non-survivors, but had no comparison of different ventilation strategies. Between Survivors (N=13) and Non-Survivors (N=31), ETCO₂ (29 ± 13 vs. 24 ± 11) and PCO₂ (39 ± 14 vs. 43 ± 14) did not differ. This study does not suggest that ventilation goal was associated with outcome, but provides evidence that characteristics of lung injury (shunt, gradient) are associated with outcome. (LOE4)

Sunde 2007, 29 is a before and after cohort study. Ventilation control with specific goals to keep pCO₂ 5-6 kPa and SaO₂ 95-98% was bundled with multiple other goals (including hypothermia and blood pressure goals). Survival increased from 26% to 56% when bundle was implemented, but it was impossible to ascertain independent effect of ventilation control separate from hypothermia, etc. (LOE3)

Suljaga-Bechtel 1984, 77 is a cohort study that compared management between survivors and nonsurvivors. There was no prospective manipulation of ventilation, but just examination of associations between outcomes and parameters. (LOE2)

Wongsurakiat 2004, 1281 is a historical comparison of practice at one hospital. This study noted that lower tidal volumes are used more in current practice, and that this strategy increased incidence of atelectasis.

However, there was no reported difference in pneumonia, oxygenation, ventilator days, or compliance. The more recent patients (who received lower tidal volumes) had higher mortality, but the authors did not feel that this was related to the ventilator strategies. (LOE3)

ANIMAL STUDIES:

Most studies in animals suggest that CO₂-reactivity of cerebral blood flow is still present in the brain after global brain ischemia. However, the magnitude of the CO₂-reactivity (%change in CBF / mmHG change in pCO₂) may be diminished or suppressed for 1-3 hours after reperfusion. The studies that report total absence of CO₂-reactivity used very prolonged periods of total cerebral ischemia. Therefore, if injury is mild-to-moderate (which represents the most salvageable situation), the literature suggests that brain is still responsive to CO₂.

One paper in dogs (11 minutes VF) reports that normocapnic ventilation improves neurological outcome relative to hypocapnic ventilation, but ventilation was part of a bundle of care including blood pressure and temperature manipulation (Safar 1996, 104). The preliminary data to devise this bundle are only available in abstract form (Ebemeyer 1994, S20). A separate study in dogs (15 minutes VF) reported fewer degenerating neurons when hypocapnia was used relative to normocapnia (Vanicky 1992, 167; Fercakova 1995, 297). The intent of hyperventilation in this paper was to reduce cerebral edema. While these papers provide opposite answers on how to titrate ventilation for an individual animal (ie. Normocapnia to promote CBF or hypocapnia to reduce cerebral edema), both papers agree that ventilation strategy can affect outcome.

Ebemeyer 1994, S20 This is NOT a full length paper, only an abstract. One group of dogs had normocapnic ventilation compared to hypocapnic ventilation, and sagittal sinus oxygen tension improved. (LOE5)

Fercakova 1995, 297. This is a follow-up ultrastructural study of the tissue from Vanick 1992, 167. It does not add to the discussion beyond Vanick 1992, 167. (LOE5)

Hossman 1973, 271 concludes that CO₂ level would not matter after prolonged cerebral ischemia in cats, because CO₂ reactivity is absent during the period of hypoperfusion. (LOE5)

Kagstrom 1983, 281 Supporting: concludes that less-injured brain regions after global ischemia in rats are still CO₂-responsive, and might therefore be injured with hypocapnia. Less-injured brain regions would be the ones that are most salvageable. (LOE5)

Krep 2000, 2866 and Krep 2000, 2873 studied CO₂ reactivity of cerebral blood flow in rats after 12 minutes of cardiac arrest. They observed a suppression (but not an absence) of CO₂ reactivity for 2-3 hours after restoration of circulation that recovered. CO₂ reactivity was still present in separate rats 7 days after cardiac arrest. (LOE5)

Nemoto 1975, 425 concludes that CO₂ level would not matter after 15 minutes of global brain ischemia in dogs. During the prolonged period of cerebral hypoperfusion, CO₂ reactivity (from 20 to 110 torr) was absent. (LOE5)

Safar 1996, 105 found that after 11 minutes of VF in dogs, a group with hypocapnia and normothermia did worse than a group with normocapnia, induced hypertension and hypothermia. The independent effects of ventilation are unknown, but the total bundle of care in the second group was intended to promote cerebral blood flow (LOE5)

Schmitz 1997, 1202 observed in rats that brain has CO₂ reactivity after 10 minutes of cardiac arrest. The magnitude of CO₂ reactivity decreased by about 30% at 1 hour of reperfusion but returned to near control at 5 hours. (LOE5)

Todd 1985, 720 observed in cats subjected to 12 minutes of VF cardiac arrest had ventilation to achieve normocapnia (40-45 torr) or hypocapnia (15-20 torr) for 3 hours. Hypocapnia reduced ICP and may have preserved CO₂-reactivity slightly more than normocapnia. The magnitude of these differences was not believed to be clinically meaningful.

Vanicky 1992, 167 observed that hyperventilation decreased the number of degenerating neurons in the brains of dogs 8 hours after 15 minutes of cardiac arrest. The result that hyperventilation resulted in fewer degenerating neurons is contrary to other papers, suggesting that hyperventilation impairs cerebral blood flow. However, this paper use a very long

period of cardiac arrest, that results in cerebral edema. In this situation, hypercapnia may have been beneficial by virtue of reducing cerebral edema. (LOE5)

Acknowledgements:

Citation List

Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in patients resuscitated from cardiac arrest. *Stroke* 1997; 28: 1569-1573

<< LOE2 (not randomized, but within-subject design) Supporting normocapnia or hypercapnia – E (indices of CBF). This was an experimental study using TCD in 10 comatose subjects Hypoventilation (ie, hypercapnia) was followed by a significant increase in MFV, a decrease in PI, and an increase in Pj_bO₂ and SjbO₂. Hyperventilation (ie, hypocapnia) did not change the MFV and PI of the MCA. However, there was a significant decrease in Pj_bO₂ and SjbO₂. Hyperventilation can decrease SjbO₂ below the ischemic threshold (55%). Strongly supports avoiding hyperventilation in order to avoid ischemia. However, ventilation was not sustained at a given level and related to long-term outcomes. >>

Ebmeyer U, Safar P, Radovsky A, Sharma C, Tanigawa K, Wang Y, Capone A, Xiao F, Bircher N, Stezoski W, Alexander H. Effective combination treatments for cerebral resuscitation from cardiac arrest in dogs: exploratory studies. *Resuscitation*. 1994;28:S20. Abstract.
<<Abstract only – Not enough detail to assess outcomes.>>

Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguía C, Nightingale P, Arroliga AC, Tobin MJ; Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA*. 2002; 287: 345-355.

<<LOE2; Concurrent controls, not randomized; This observational cohort looked at 28 day mortality (C) . The cohort of 15757 patients included a subset of 100 subjects with ventilation as a consequence of cardiac arrest. While cardiac arrest and coma had independent associations with mortality, there were also independent effects of high peak (>50 mmHg) and plateau pressures (>35 mmHg). Tidal volume and PEEP did not have independent effects in the multivariable model.>>

Fercáková A, Vanicky I, Marsala M, Marsala J. Effect of prolonged hyperventilation on ischemic injury of neurons after global brain ischemia in the dog. *J Hirnforsch*. 1995; 36:297-304.

<<LOE5 Supportive. This is a follow-up ultrastructural study of the tissue from Vanick 1992, 167. It does not add to the discussion beyond Vanicky 1992, 167.>>

Helpaer MA, Kirsch JR, Haun SE, Koehler RC, Traystman RJ. Age-related cerebrovascular reactivity to CO₂ after cerebral ischemia in swine. *Am J Physiol*. 1991;260: H1482-H1488.

<<LOE5 (animal study). Supportive. The CO₂ reactivity of cerebral blood flow is impaired for <120 minutes after 10 minutes of cerebral ischemia in swine, and recovers more quickly in older swine than in younger swine>>

Hossman KA, Lechtape-Gruter H, Hossman V. The role of cerebral blood flow for the recovery of the brain after prolonged ischemia. *Z Neurol* 1973; 204: 281-299

ABSTRACT NOT AVAILABLE

<<LOE 5 (animal study). Opposing: concludes that CO₂ level would not matter. In cats, CO₂ reactivity is absent during the period of hypoperfusion.>>

Kågström E, Smith M, Siesjö BK. Cerebral circulatory responses to hypercapnia and hypoxia in the recovery period following complete and incomplete cerebral ischemia in the rat. *Acta Physiol Scand*. 1983;118:281-291

<<LOE5 (animal study): Supporting: concludes that less-injured brain regions are still CO₂-responsive, and might therefore be injured with hypocapnia. Less-injured brain regions would be the ones most salvageable. >>

Koch KA, Jackson DL, Schmiedl M, Rosenblatt JI. Total cerebral ischemia: effect of alterations in arterial PCO₂ on cerebral microcirculation. J Cereb Blood Flow Metab. 1984;4:343-349

<<LOE5 (animal study). Supportive. The CO₂ reactivity of cerebral blood flow is impaired for 1-3 hours, but recovers after 12 minutes of cerebral ischemia in >>

Krep H, Brinker G, Pillekamp F, Hossmann KA. Treatment with an endothelin type A receptor-antagonist after cardiac arrest and resuscitation improves cerebral hemodynamic and functional recovery in rats. Crit Care Med. 2000 Aug;28(8):2866-72.

<<LOE 5 – animal study – Supporting, IN RATS, CO₂ reactivity after 12 minutes of cardiac arrest is suppressed, but not absent for 2-3 hour, then recover>>

Krep H, Brinker G, Schwindt W, Hossmann KA. Endothelin type A-antagonist improves long-term neurological recovery after cardiac arrest in rats. Crit Care Med. 2000 Aug;28(8):2873-80.

<<LOE 5 – animal study – In rats, CO₂ reactivity is present at 7 days after 12 minutes cardiac arrest>>

Moon SW, Lee SW, Choi SH, Hong YS, Kim SJ, Kim NH. Arterial minus end-tidal CO₂ as a prognostic factor of hospital survival in patients resuscitated from cardiac arrest. Resuscitation. 2007 Feb;72(2):219-25. Epub 2006 Nov 13.

<< LOE 4; Neutral; Good study; Compared survivors to non-survivors, but had no comparison of different ventilation strategies. Does not suggest that ventilation goal was associated with outcome. Rather provides evidence that characteristics of lung injury (shunt, gradient) are associated with outcome. Prospective cohort study of patients with pulse after CPR. Between Survivors (N=13) and Non-Survivors (N=31), ETCO₂ (29 ± 13 vs. 24 ± 11) and PCO₂ (39 ± 14 vs. 43 ± 14) did not differ. >>

Nemoto EM, Snyder JV, Carroll RG, Morita H. Global ischemia in dogs: cerebrovascular CO₂ reactivity and autoregulation. Stroke. 1975;6: 425-431.

<<LOE5 (animal study). Opposing: Concludes that CO₂ level would not matter. In dogs, with 15 minutes of global brain ischemia induced by occlusion of aorta and vena cava, cerebral blood flow is transiently increased (hyperemia) followed by a prolonged period of hypoperfusion. During this period of hypoperfusion, CO₂ reactivity (from 20 to 110 torr) was absent. >>

Safar P, Xiao F, Radovsky A, Tanigawa K, Ebmeyer U, Bircher N, Alexander H, Stezoski SW. Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. Stroke. 1996; 27:105-13.

<<LOE5 (animal study) Supportive, but poorly addresses this question: too many variable differ between groups. After 11 minutes of VF in dogs, a group with hypocapnia and normothermia did worse than a group with normocapnia, induced hypertension and hypothermia. The independent effects of ventilation are unknown, but the total bundle of care in the second group was intended to promote cerebral blood flow>>

Schmitz B, Böttiger BW, Hossmann KA. Functional activation of cerebral blood flow after cardiac arrest in rat. J Cereb Blood Flow Metab. 1997 Nov;17(11):1202-1209.

<<LOE 5 – animal study, Supporting, In rats, this study confirms that brain has CO₂ reactivity after cardiac arrest. The magnitude of CO₂ reactivity decreased by about 30% at 1 hour of reperfusion but returned to near control at 5 hours. >>

Suljaga-Pechtcl K, Goldberg E, Strickon P, Berger M, Skovron ML. Cardiopulmonary resuscitation in a hospitalized population: prospective study of factors associated with outcome. Resuscitation. 1984; 12: 77-95.

<< LOE2 (nonrandomized) Supportive. No manipulation of ventilation – just examination of associations between outcomes and parameters.>>

Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, Draegni T, Steen PA. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*. 2007 Apr;73(1):29-39. Epub 2007 Jan 25.

<< LOE 3. BEFORE AND AFTER PROSPECTIVE COHORT. POOR for worksheet question, because it is impossible to ascertain independent effect of ventilation control separate from hypothermia, etc.. Ventilation control was bundled with multiple other goals. Ventilator was adjusted to keep pCO₂ 5-6 kPa, SaO₂ 95-98. 26% -> 56%.survival when bundle was implemented. >>

Todd MM, Tommasino C, Shapiro HM Cerebrovascular effects of prolonged hypocarbia and hypercarbia after experimental global ischemia in cats. *Crit Care Med*. 1985; 13:720-723.

<<LOE 5 (animal study). Neutral: there were numerical, but no meaningful differences in physiological measurements during the first 3 hours. This study assigned cats subjected to 12 minutes of VF cardiac arrest had ventilation to achieve normocapnia (40-45 torr) or hypocapnia (15-20 torr) for 3 hours. Hypocapnia reduced ICP and may have preserved CO₂-reactivity slightly more than normocapnia. The magnitude of these differences was not believed to be clinically meaningful. Long-term outcomes were not examined.

Vanicky I, Marsala M, Murar J, Marsala J. Prolonged postischemic hyperventilation reduces acute neuronal damage after 15 min of cardiac arrest in the dog. *Neurosci Lett*. 1992;135:167-170.

<<LOE5 (animal study). This paper only followed dogs for 8 hours. The result that hyperventilation resulted in fewer degenerating neurons is contrary to other papers, suggesting that hyperventilation impairs cerebral blood flow. However, this paper use a very long period of cardiac arrest, that results in cerebral edema. In this situation, hypercapnia may have been beneficial by virtue of reducing cerebral edema. Even though this paper advocates for hyperventilation, it is supportive of the worksheet question, because there is evidence that the ventilation strategy affects outcome.>>

Wongsurakiat P, Pierson DJ, Rubinfeld GD. Changing pattern of ventilator settings in patients without acute lung injury: changes over 11 years in a single institution. *Chest*. 2004; 126: 1281-1291.

<<LOE 3 – Historical comparisons of practice – outcomes C, E (Supportive of conclusion that ventilator strategy matters – Noted that lower tidal volumes are used more in current practice, and that this strategy increased incidence of atelectasis. However, there was no reported difference in pneumonia, oxygenation, ventilator days, or compliance. The more recent patients (who received lower tidal volumes) had higher mortality, but the authors did not feel that this was related to the ventilator strategies. >>

PAPERS REVIEWED BUT NOT INCLUDED:

Beckstead JE. Tweed WA. Lee J. MacKeen WL. Cerebral blood flow and metabolism in man following cardiac arrest. *Stroke*. 1978; 9: 569-573

<< NO DATA ON VENTILATION MANIPULATION – DO NOT INCLUDE Cohort study of patients admitted with pulse after CPR. Ventilation was controlled to eucapnia. Examined cerebral blood flow. There was little variation in pCO₂, resulting in little opportunity for relating ventilator management to outcome. No control group. No data to address question. Do not include. >>

Buunk G, van der Hoeven JG, Frölich M, Meinders AE. Cerebral vasoconstriction in comatose patients resuscitated from a cardiac arrest? *Intensive Care Med*. 1996;22:1191-1196

<<NO DATA ON VENTILATION MANIPULATION – DO NOT INCLUDE>>

van der Hoeven JG, de Koning J, Compier EA, Meinders AE. Early jugular bulb oxygenation monitoring in comatose patients after an out-of-hospital cardiac arrest. *Intensive Care Med*. 1995 Jul;21(7):567-72.

<< NO STUDY OF VENTILATION STRATEGY - DO NOT INCLUDE – does not address worksheet question. Cohort study compared survivors and non-survivors. SjbO₂ and Djbo₂ (A-V difference) during first few hours after cardiac arrest did no differ >>

Weil MH. Ruiz CE. Michaels S. Rackow EC. Acid-base determinants of survival after cardiopulmonary resuscitation. Care Medicine. 1985; 13: 888-92,

<< NO STUDY OF VENTILATION STRATEGY - DO NOT INCLUDE - observational cohort study. No manipulation of ventilation. Primary analysis concerns alkalemia. Does not address worksheet question – Exclude. >>