

## WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

### Worksheet author(s)

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### Clinical question.

In neonates requiring resuscitation and not responding to CPR (P) does the administration of sodium bicarbonate (I) versus no bicarbonate (C) improve outcome (O)

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

**State if this is a proposed new topic or revision of existing worksheet:** Second update

### 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).

Ovid, Medline from 2004-2008 Mesh terms Neonates and/or resuscitation and/or CPR and sodium bicarbonate and/or asphyxia and/or infant and/or delivery room. Relevant hits: infant and/or newborn and bicarbonate (17 hits), sodium bicarbonate and delivery room + resuscitation (165 hits), sodium bicarbonate + delivery room (4 hits) - Two new studies retrieved  
 Embase from 2004 to 2008 Same terms and combinations – same two studies retrieved  
 Cochrane library – one review found CD004864 2006  
 ECC endnote library –no new study found  
 References from the most recent review articles

### • State inclusion and exclusion criteria

Any neonatal study related to sodium bicarbonate administration during acute cardiac arrest, neonatal animal studies. Non English language articles were searched

### • Number of articles/sources meeting criteria for further review:

Two new articles were found that met criteria for review and inclusion in the worksheet. Thus there are now 23 articles contained in the worksheet

## Summary of evidence

### Evidence Supporting Clinical Question

In neonates requiring resuscitation and not responding to CPR(P) does the administration of sodium bicarbonate (I) versus no bicarbonate (C) improve outcome(O)

<b>Good</b>					<i>Bar-Joseph, 1998<sup>A</sup></i>
<b>Fair</b>					<i>Leong, 2001,<sup>A</sup> Vukmir, 1995<sup>AB</sup> Neumar, 1995<sup>E</sup> Rubertsson, 1993<sup>E</sup></i>
<b>Poor</b>					<i>Sessler, 1987,<sup>E</sup> Preziosi, 1993,<sup>E</sup></i>
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
<b>Level of evidence</b>					

A = Return of spontaneous circulation

B = Survival of event

C = Survival to hospital discharge

D = Intact neurological survival

E = Other endpoint

*Italics = Animal studies*

Blue= Adult studies

## Evidence Neutral to Clinical question

In neonates requiring resuscitation and not responding to CPR(P) does the administration of sodium bicarbonate (I) versus no bicarbonate (C) improve outcome(O)

<b>Good</b>					Dybvik, 1995* <sup>BDE</sup>
<b>Fair</b>	Lokesh, L 2004 <sup>CDE</sup> Beveridge, 2006 Murki, S 2004 <sup>E</sup>				Levy, 1998 <i>Bleske, 1992,</i> <sup>E</sup>
<b>Poor</b>					<i>Guerci, 1986,</i> <i>Federiuk 1991,</i> <sup>E</sup> <i>Laptook, 1985,</i> <sup>E</sup> <i>Wheeler, 1979</i> <sup>E</sup>
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
<b>Level of evidence</b>					

A = Return of spontaneous circulation

C = Survival to hospital discharge

E = Other endpoint

B = Survival of event

D = Intact neurological survival

*Italics = Animal studies*

Blue= Adult studies

## Evidence Opposing Clinical Question

<b>Good</b>					
<b>Fair</b>					Levy, 1998 <i>Kette, 1991,</i> <sup>E</sup> <i>Wiklund, 1990,</i>
<b>Poor</b>					Cooper, 1990, <sup>E</sup> Bishop 1976 <sup>E</sup>  Simmons 1974 <sup>E</sup> Lou, 1978 <sup>E</sup>
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
<b>Level of evidence</b>					

A = Return of spontaneous circulation

C = Survival to hospital discharge

E = Other endpoint

B = Survival of event

D = Intact neurological survival

*Italics = Animal studies*

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

The role of sodium bicarbonate during resuscitation remains controversial. There are concerns that in the absence of adequate ventilation, sodium bicarbonate administration can exacerbate intracellular hypercarbia worsening intracellular acidosis. Moreover as a secondary consequence either directly or indirectly, there may be impaired myocardial function. In the premature infant infusion of sodium bicarbonate may result in the development of intraventricular hemorrhage (Simmons, 1974)(LOE 5). There is a small randomized neonatal study in “asphyxiated “ term infants (low five minute Apgar score and requiring bag/mask positive pressure ventilation that failed to demonstrate any beneficial effect of sodium bicarbonate administration on neurologic outcome or survival (Lokesh, 2004, Beveridge, 2006)(LOE 1). Thus there was no effect on mortality prior to discharge [Relative risk (RR) 1.04 (95% confidence interval (CI) 0.49 to 2.21)], abnormal neurological examination at discharge [RR 0.86 (95% CI 0.30 to 2.50)] or a composite outcome of death or abnormal neurological examination at discharge [RR 0.97 (95% confidence interval 0.59 to 1.60)], incidence of encephalopathy [RR 1.30 (95% CI 0.88 to 1.92)], IVH [RR 1.04 (95% CI 0.23 to 4.70)] and neonatal seizures [RR 1.19 (95% CI 0.50 to 2.82)] noted. A recent studies failed to demonstrate any benefit from sodium bicarbonate administration on acid base status in the 24 hours following infusion (Murki (2004)(LOE 1). There are no neonatal animal studies that have addressed the specific role of bicarbonate in achieving recovery of spontaneous circulation or survival following CPR. A tangential neonatal animal study has noted attenuated hemodynamic responses to resuscitation with epinephrine and oxygen when concomitant acidosis was present (Preziosi, 1993)(LOE 5). However this model used a pure metabolic acidosis that is distinct from the mixed acidosis noted in the delivery room. In addition, acidosis was produced by the infusion of exogenous lactate, which may not adequately simulate acidosis derived from intracellular acid production as a result of cellular hypoxia.

Additional neonatal studies suggest that bicarbonate administration increases arterial pH, brain intracellular pH and PaCO<sub>2</sub> without producing concomitant paradoxical brain intracellular acidosis provided adequate cardiac output is maintained (Sessler, 1987 Laptook, 1985)(LOE 5). However one neonatal human study reported significant reduction in cerebral blood flow (up to 50%) following bicarbonate infusion (Lou, 1978)(LOE 5). An evidence-based review of adult human and animal studies indicates that no human study has demonstrated a beneficial impact on survival and that several adult human studies (level of evidence 3 and 4) demonstrated deleterious effects on physiologic endpoints from the administration of bicarbonate during CPR (Levy, 1998). While several animal studies demonstrated impaired function in response to bicarbonate administration during CPR (Guerci, 1986, Wiklund, 1990, {Kette, 1991, Federiuk, 1991, Rubertsson, 1993, Neumar, 1995)(LOE 5) others have demonstrated survival benefit from the administration of bicarbonate during CPR (Bar Joseph 1998, Bleske, 1992 Leong, 2001 Vukmir, 1995)(LOE 5). In summarizing the clinical and animal observations, given the known and potential side effects of sodium bicarbonate infusions including depression of myocardial function from the osmolar load, paradoxical intracellular acidosis, reduction in cerebral blood flow and the risk for intraventricular hemorrhage, the use of sodium bicarbonate infusion should be discouraged during brief CPR, but sodium bicarbonate may be of some benefit in an infant with prolonged CPR unresponsive to other therapy including adequate ventilation.

**Acknowledgements:**

## *Citation List*

- {Beveridge, 2006 #22} Beveridge, C. J. Wilkinson, A. R. Sodium bicarbonate infusion during resuscitation of infants at birth Cochrane Database of Systematic Reviews 2006 CD004864
- {Lokesh, 2004 #207} Lokesh L, Kumar P, Murkai S et al A randomized controlled trial of sodium bicarbonate in neonatal resuscitation-effect on immediate outcome. Resuscitation 2004 60(2): 219-23.
- {Lou, 1978 #39} Lou, H. C., N. A. Lassen, et al. Decreased cerebral blood flow after administration of sodium bicarbonate in the distressed newborn infant. Acta Neurol Scand 1978 57(3): 239-47.
- {Simmons, 1974 #44} Simmons, M. A., E. W. Adcock, 3rd, et al. (1974). "Hyponatremia and intracranial hemorrhage in neonates. N Engl J Med 291(1): 6-10.
- {Laptook, 1985 #37} Laptook, A. R. The effects of sodium bicarbonate on brain blood flow and O<sub>2</sub> delivery during hypoxemia and acidemia in the piglet. Pediatr Res 1985; 19(8): 815-9.
- {Murki, 2004 #23} Murki, S. Kumar, P. Lingappa, L. Narang, A. Effect of a single dose of sodium bicarbonate given during neonatal resuscitation at birth on the acid-base status on first day of life Journal of Perinatology 2004;24: 696-9
- {Preziosi, 1993 #203} Preziosi, M. P., J. C. Roig, et al Metabolic acidemia with hypoxia attenuates the hemodynamic responses to epinephrine during resuscitation in lambs. Crit Care Med 1993; 21(12): 1901-7.
- {Sessler, 1987 #38} Sessler, D., P. Mills, et al. Effects of bicarbonate on arterial and brain intracellular pH in neonatal rabbits recovering from hypoxic lactic acidosis. J Pediatr 1987; **111**(6 Pt 1): 817-23.
- {Wheeler, 1979 #201} Wheeler, A. S., S. Sadri, et al. Intracranial hemorrhage following intravenous administration of sodium bicarbonate or saline solution in the newborn lamb asphyxiated in utero Anesthesiology 1979 ; **51**(6): 517-521.
- {Bishop, 1976 #31} Bishop, R. L. and M. L. Weisfeldt . Sodium bicarbonate administration during cardiac arrest. Effect on arterial pH PCO<sub>2</sub>, and osmolality. JAMA 1976; 235(5): 506-9.
- {Cooper, 1990 #41} Cooper, D. J., K. R. Walley, et al. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. Ann Intern Med 1990;112(7): 492-8.
- {Dybvik, 1995 #204} Dybvik, T., T. Strand, et al. Buffer therapy during out-of-hospital cardiopulmonary resuscitation. Resuscitation 1995;29(2): 89-95.
- {Levy, 1998 #206} Levy, M. M. An evidence-based evaluation of the use of sodium bicarbonate during cardiopulmonary resuscitation. Crit Care Clin 1998; 14(3): 457-83.
- {Bar-Joseph, 1998 #36} Bar-Joseph, G., T. Weinberger, et al Comparison of sodium bicarbonate, Carbicarb, and THAM during cardiopulmonary resuscitation in dogs. Crit Care Med 1998; 26(8): 1397-408.
- {Bleske, 1992 #200} Bleske, B. E., M. S. S. Chow, et al. Effects of different dosages and modes of sodium bicarbonate administration during cardiopulmonary resuscitation. American Journal of Emergency Medicine 1992;10(6): 525-532.
- {Guerci, 1986 #32} Guerci, A. D., N. Chandra, et al. Failure of sodium bicarbonate to improve resuscitation from ventricular fibrillation in dogs. Circulation 1986 ; 74(6 Pt 2): IV75-9.
- {Federiuk, 1991 #40} Federiuk, C. S., A. B. Sanders, et al. The effect of bicarbonate on resuscitation from cardiac arrest. Ann Emerg Med 1991; 20(11): 1173-7.
- {Kette, 1991 #33} Kette, F., M. H. Weil, et al. Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion pressure. Jama 1991; 266(15): 2121-6.
- {Leong, 2001 #197} Leong, E. C. M., J. C. Bendall, et al. Sodium bicarbonate improves the chance of resuscitation after 10 minutes of cardiac arrest in dogs. Resuscitation 2001; 51(3): 309-315.

- {Neumar, 1995 #35} Rubertsson, 1993 #34} Neumar, R. W., N. G. Bircher, et al. Epinephrine and sodium bicarbonate during CPR following asphyxial cardiac arrest in rats. *Resuscitation* 1995; 29(3): 249-63.
- Rubertsson, 1993 #34} Rubertsson, S. and L. Wiklund . Hemodynamic effects of epinephrine in combination with different alkaline buffers during experimental, open-chest, cardiopulmonary resuscitation. *Crit Care Med*1993;21(7): 1051-7.
- {Vukmir, 1995 #199} Vukmir, R. B., N. G. Bircher, et al. Sodium bicarbonate may improve outcome in dogs with brief or prolonged cardiac arrest. *Critical Care Medicine* 1995; 23(3): 515-522.
- {Wiklund, 1990 #43} Wiklund, L., G. Ronquist, et al. Effects of alkaline buffer administration on survival and myocardial energy metabolism in pigs subjected to ventricular fibrillation and closed chest CPR. *Acta Anaesthesiol Scand* 1990;34(6): 430-9.

### Neonatal Clinical Studies

Beveridge, C. J. Wilkinson, A. R. Sodium bicarbonate infusion during resuscitation of infants at birth Cochrane Database of Systematic Reviews 2006 CD004864

Comment This is a Cochrane review of the Lokesh study (see below) the only randomized study evaluating the role of sodium bicarbonate infusion during resuscitation

**Level of Evidence 1-Quality Fair- Neutral**

\* Lokesh, L.Kumar, P.Murki, S.Narang, A A randomized controlled trial of sodium bicarbonate in neonatal resuscitation--effect on immediate outcome. *Resuscitation* 2004;60:219-223

Comment Small randomized study that shows no benefit to the administration of sodium bicarbonate during resuscitation of the largely premature infant.

**Level of Evidence 1- Quality Fair- Neutral**

Lou, H. C.Lassen, N. A. Fris-Hansen, B Decreased cerebral blood flow after administration of sodium bicarbonate in the distressed newborn infant *Acta Neurol Scand* 1978; 57:239-247

### Contents

Methods In the course of studies on cerebral blood flow in newborn infants the effect of sodium bicarbonate infusion on cerebral blood flow was noted. Cerebral blood flow was measured utilizing the 133 Xe clearance technique before and after the treatment with 1 to 8 meqs of sodium bicarbonate in seven distressed newborn infants. Results In six of the seven cases a decrease in cerebral blood flow was noted, which in most cases range of reduction was 14 to 22 ml/100 g/min, which is about half the value prior to the bicarbonate infusion. In one case an extreme reduction occurred: cerebral blood flow was reduced to 3 ml/100 g/min, well below the level compatible with tissue survival.

Comments.The reduction in CBF may be secondary to bicarbonate induced cerebral vasoconstriction. The clinical implications of these observations are unclear.

**Level of Evidence 5 - Quality Fair- Opposing**

Murki, S.Kumar, P.Lingappa, L.Narang, A. Effect of a single dose of sodium bicarbonate given during neonatal resuscitation at birth on the acid-base status on first day of life *Journal of Perinatology* 2004;24: 696-9

**Comment.** No effect of sodium bicarbonate infusion

**Level of Evidence 1-Quality Fair- Neutral**

Simmons, M. A.Adcock, E. W., 3<sup>rd</sup> Bard, H. Battaglia, F. C. Hyponatremia and intracranial hemorrhage in neonates *N Engl J Med* 1974;291: 6-10

Comments: The retrospective nature of the study in addition to establishing a diagnosis at autopsy precludes any definitive conclusions to be inferred from this data other than the association between two events.

**Level of Evidence 5 - Quality Fair - Opposing**

Neonatal Animal Studies

Laptook, A. R. The effects of sodium bicarbonate on brain blood flow and O<sub>2</sub> delivery during hypoxemia and acidemia in the piglet  
Pediatr Res 1985;19

Comment- Correction of metabolic acidosis does not appear to alter brain blood flow or oxygen delivery

**Level of Evidence 5-Quality Good –Neutral**

Preziosi, M. P.Roig, J. C.Hargrove, N. Burchfield, D. J. Metabolic acidemia with hypoxia attenuates the hemodynamic responses to epinephrine during resuscitation in lambs Crit Care Med 1993;21:1901-1907

Comment Positive effect of correcting acidosis demonstrated on cardiovascular status. Note the PCO<sub>2</sub> was maintained 35 to 45mmHg. Again, I think it is interesting that no adverse effect of the exogenous acid administration was seen until they also made the lamb hypoxic compromising cardiac contractility. I really think this model is flawed with exogenous acid administration.

**Level of Evidence 5-Quality Fair - Supportive**

Sessler, D.Mills, P.Gregory, G.Litt, L.James, T. Effects of bicarbonate on arterial and brain intracellular pH in neonatal rabbits recovering from hypoxic lactic acidosis J Pediatr 1987;111:817-823

Comments Sodium bicarbonate infusion increased control pH, PCO<sub>2</sub> as well as increasing brain intracellular pH. The “so called “ paradoxical intracellular acidosis did not occur, however the bicarbonate was infused in the presence of adequate perfusion and ventilation.

**Level of Evidence 5-Quality Good - Supportive**

Wheeler, A. S. Sadri, S. Gutsche, B. B. et al. Intracranial hemorrhage following intravenous administration of sodium bicarbonate or saline solution in the newborn lamb asphyxiated in utero Anesthesiology 1979;51: 517-521

Comments Neonatal animal study that does not demonstrate a relationship to IVH. However the sheep model is distinctly different from the premature infant with a germinal matrix.

**Level of Evidence 5-Quality Good - Neutral**

Adult Clinical Studies

Bishop, R. L.Weisfeldt, M. L. Sodium bicarbonate administration during cardiac arrest. Effect on arterial pH PCO<sub>2</sub>, and osmolality JAMA 1976;235:506-509

Comments These studies demonstrate that (1) in the absence of preexisting acidosis, severe acidosis can be prevented by adequate ventilation alone; (2) sodium bicarbonate administration results in a significant rise in arterial PCO<sub>2</sub>, which parallels the rise in pH despite adequate ventilation; (3) during prolonged cardiac resuscitation, there is a rise in arterial osmolality that is accentuated by sodium bicarbonate.

Furthermore these studies suggest that sodium bicarbonate should not be used during resuscitation (1) in the absence of effective hyperventilation or where carbon dioxide removal is inadequate despite adequate ventilation, (2) in repeated doses, without confirmation of substantial acidosis, or (3) when cardiac arrest has been of brief duration and preexisting acidosis is unlikely.

**Level of Evidence 5 -Quality Fair – Opposing**

Cooper, D. J.Walley, K. R.Wiggs, B. R.Russell, J. A. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study Ann Intern Med 1990;42:492-498

Comments: Small study. Strengths include randomized blinded and crossover.

**Level of Evidence 5-Quality Good – Opposing**

\* Dybvik, T.Strand, T.Steen, P. A Buffer therapy during out-of-hospital cardiopulmonary resuscitation Resuscitation 1995;29:89-95

Comments Randomized adult study of bicarbonate versus saline in asystolic out of hospital patient of whom one third in both groups were admitted to the ICU. Logistic modeling showed no improvement in outcome with buffer therapy. This is the only human randomized study addressing this specific question

#### **Level of Evidence 5-Quality Excellent - Neutral**

##### Evidenced Based Review of Adult Clinical and Experimental Studies

- \* Levy, M. M. An evidence-based evaluation of the use of sodium bicarbonate during cardiopulmonary resuscitation. Crit Care Clin 14(3): 457-83.

The author's conclusions included the following:

- 1) No human study has demonstrated a beneficial impact on survival
- 2) Several adult human studies (level 3 and 4) have demonstrated deleterious effects on physiologic end points from the administration of bicarbonate during CPR
- 3) Several animal studies have demonstrated impaired function in response to bicarbonate administration during CPR
- 4) Several animal studies (n=4) have demonstrated survival benefit from the administration of bicarbonate during CPR

#### **Level of Evidence 5 -Quality Fair - Neutral**

##### Adult Animal Studies

Bar-Joseph, G., T. Weinberger, et al. Comparison of sodium bicarbonate, Carbicab and THAM during cardiopulmonary resuscitation in dogs. 1998 Crit Care Med 26: 1397-408.

**Comments** Buffer therapy promoted successful resuscitation after prolonged cardiac arrest, regardless of coronary perfusion pressure. NaHCO<sub>3</sub>, and to a lesser degree, Carbicarb, was beneficial in promoting early return of spontaneous circulation. When epinephrine was used to promote tissue perfusion, there was no evidence for hypercarbic venous acidosis associated with the use of these CO<sub>2</sub> generating buffers. This study demonstrated a positive benefit of sodium bicarbonate therapy

#### **Level of Evidence 5- Quality Good- Supportive**

Bleske, B. E., M. S. S. Chow, et al. Effects of different dosages and modes of sodium bicarbonate administration during cardiopulmonary resuscitation. American Journal of Emergency Medicine 1992 10: 525-532.

**Comments** These observations suggest that if administration of sodium bicarbonate was contemplated a continuous infusion may be the most desirable mode of administration for the prevention of venous acidosis during CPR

Level of Evidence 5-Quality Good - Neutral

Guerci, A. D.Chandra, N.Johnson, E. et al Failure of sodium bicarbonate to improve resuscitation from ventricular fibrillation in dogs Circulation 1986;74(Suppl IV) 75-79

**Comments** The data do not suggest a primary role for sodium bicarbonate in resuscitation following ventricular fibrillation in adult dogs. The relevance to the neonate who presents with bradycardia is unclear.

#### **Level of Evidence 5- Quality Fair- Neutral**

Federiuk, C. S. Sanders, A. B. Kern, K. B et al The effect of bicarbonate on resuscitation from cardiac arrest Ann Emerg Med 1991;20: 1173-77

**Comments** The use of sodium bicarbonate did not improve resuscitation from prolonged cardiac arrest

#### **Level of Evidence 5-Quality Fair - Neutral**

Kette, F.Weil, M. H.Gazmuri, R. J. Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion pressure JAMA 1991;266:2121-6

**Comments** Sodium bicarbonate solution in the absence of vasopressor agents may adversely affect cardiac resuscitation by reducing the coronary perfusion pressure below critical thresholds.

#### **Level of Evidence 5-Quality Fair**

Leong, E. C. M., J. C. Bendall, et al. Sodium bicarbonate improves the chance of resuscitation after 10 minutes of cardiac arrest in dogs. *Resuscitation* 2001; 51: 309-315.

**Comments** These data suggest that following prolonged arrest, bicarbonate therapy and a period of perfusion prior to defibrillation may increase survival. However longer-term outcome and in particular CNS outcome is not provided. There is biochemical, histological and clinical evidence that the cumulative energy dose delivered to the myocardium during defibrillation attempts is associated with myocardial damage, which decreases the likelihood of successful resuscitation. This is not a concern to the neonatal population

**Level of Evidence 5-Quality Fair**

Neumar, R. W., N. G. Bircher, et al. Epinephrine and sodium bicarbonate during CPR following asphyxial cardiac arrest in rats. *Resuscitation* 1995; 29: 249-63.

**Level of Evidence 5 - Quality Fair- supportive**

Rubertsson, S. Wiklund, L. Hemodynamic effects of epinephrine in combination with different alkaline buffers during experimental, open-chest, cardiopulmonary resuscitation. *Crit Care Med* 1993; 21: 1051-57

Comments Combination of high dose epinephrine and sodium bicarbonate produced lower systemic blood pressure

**Level of Evidence 5-Quality Fair- Supportive**

Vukmir, R. B., N. G. Bircher, et al. Sodium bicarbonate may improve outcome in dogs with brief or prolonged cardiac arrest. *Critical Care Medicine* 1995 23: 515-522.

Comments The empirical administration of bicarbonate improves the survival rate and neurologic outcome in a canine model of cardiac arrest. These observations support the current recommendation of sodium bicarbonate administration following prolonged resuscitation in the face of adequate ventilation

**Level of Evidence 5-Quality Fair- Supportive**

Wiklund, L. Ronquist, G. Stjernstrom, H. Waldenstrom, A Effects of alkaline buffer administration on survival and myocardial energy metabolism in pigs subjected to ventricular fibrillation and closed chest CPR *Acta Anaesthesiol Scand* 1990;34: 430-439

Comments Sodium bicarbonate infusion was associated with higher PCO<sub>2</sub> .

**Level of Evidence 5-Quality Fair - Opposing**