WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

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[redacted]

2. Clinical question:

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

3. Conflict of interest specific to this question:

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

4. Search strategy (including electronic databases searched):

4a. Databases

MEDLINE via PubMed (1948 to March 2011) (performed on April 10, 2011; updated 5/22/11) using clinical queries filter for therapy/broad and systematic reviews

1. bicarbonate
2. buffer
3. buffering
4. asystole
5. cardiac arrest
6. resuscitation
7. cardiopulmonary arrest

1 and 4: 37 relevant hits out of 370 total hits

Search details:
systematic[sb] AND (("bicarbonates"[MeSH Terms] OR "bicarbonates"[All Fields] OR "bicarbonate"[All Fields]) AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields] OR "asystole"[All Fields])) AND English[lang]
Therapy/Broad[filter] AND (("bicarbonates"[MeSH Terms] OR "bicarbonates"[All Fields] OR "bicarbonate"[All Fields]) AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields] OR "asystole"[All Fields])) AND English[lang]

2 and 4: 1 additional relevant hit out of 353 total hits

Search details:
Therapy/Broad[filter] AND (("buffers"[MeSH Terms] OR "buffers"[All Fields] OR "buffer"[All Fields] OR "buffers"[Pharmacological Action]) AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields] OR "asystole"[All Fields])) AND English[lang]

3 and 4: no additional relevant hits out of 12 total hits

Search details:

Therapy/Broad[filter] AND (buffering[All Fields] AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields] OR "asystole"[All Fields])) AND English[lang]

systematic[sb] AND (buffering[All Fields] AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields] OR "asystole"[All Fields])) AND English[lang]
Medical Genetics[filter] AND (buffering[All Fields] AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields] OR "asystole"[All Fields])) AND English[lang]

1 and 5: 1 additional relevant hits of 410 total hits
Search details:

Therapy/Broad[filter] AND (("bicarbonates"[MeSH Terms] OR "bicarbonates"[All Fields] OR "bicarbonate"[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])) AND English[lang]
systematic[sb] AND (("bicarbonates"[MeSH Terms] OR "bicarbonates"[All Fields] OR "bicarbonate"[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])) AND English[lang]

2 and 5: 0 additional relevant hits of 413 total hits
Search details:
Therapy/Broad[filter] AND (("buffers"[MeSH Terms] OR "buffers"[All Fields] OR "buffer"[All Fields] OR "buffers"[Pharmacological Action]) 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])) AND English[lang]
systematic[sb] AND (("buffers"[MeSH Terms] OR "buffers"[All Fields] OR "buffer"[All Fields] OR "buffers"[Pharmacological Action]) 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])) AND English[lang]
Medical Genetics[filter] AND (("buffers"[MeSH Terms] OR "buffers"[All Fields] OR "buffer"[All Fields] OR "buffers"[Pharmacological Action]) 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])) AND English[lang]

3 and 5: no additional relevant hits
Search details:
Therapy/Broad[filter] AND (buffering[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])) AND English[lang]
systematic[sb] AND (buffering[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])) AND English[lang]
Medical Genetics[filter] AND (buffering[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])) AND English[lang]

1 and 6: 8 additional relevant hits of 776 hits
Search details:
("bicarbonates"[MeSH Terms] OR "bicarbonates"[All Fields] OR "bicarbonate"[All Fields]) AND ("resuscitation"[MeSH Terms] OR "resuscitation"[All Fields]) AND English[lang]

2 and 6: 2 additional relevant hits of 509 hits
Search details:
("buffers"[MeSH Terms] OR "buffers"[All Fields] OR "buffer"[All Fields] OR "buffers"[Pharmacological Action]) AND ("resuscitation"[MeSH Terms] OR "resuscitation"[All Fields]) AND English[lang]

3 and 6: 0 additional relevant hit of 36 hits
Search details:

buffering[All Fields] AND ("resuscitation"[MeSH Terms] OR "resuscitation"[All Fields]) AND English[lang]

1 and 7: 0 additional relevant hits of 374 hits
Search details:
("bicarbonates"[MeSH Terms] OR "bicarbonates"[All Fields] OR "bicarbonate"[All Fields]) AND ("heart arrest"[MeSH Terms] OR ("cardiopulmonary"[All Fields] AND "arrest"[All Fields]) OR "cardiopulmonary arrest"[All Fields]) AND English[lang]

2 and 7: 0 additional relevant hits of 162 hits
Search details:
("buffers"[MeSH Terms] OR "buffers"[All Fields] OR "buffer"[All Fields] OR "buffers"[Pharmacological Action]) AND (("cardiopulmonary"[All Fields] AND "arrest"[All Fields]) OR "cardiopulmonary arrest"[All Fields])
3 and 7: 0 additional relevant hits of hits
Search details:
buffering[All Fields] AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields] OR ("cardiopulmonary"[All Fields] AND "arrest"[All Fields]) OR "cardiopulmonary arrest"[All Fields])

CAB via OvidSP 4/18/11

1 and 4: no hits
2 and 4: no hits
3 and 4: no hits
1 and 5: 0 additional relevant hits of 9 hits
2 and 5: no hits
3 and 5: 0 additional relevant hits of 1 hit
1 and 6: 0 additional relevant hits of 16 hits
2 and 6: 0 additional relevant hits of 2 hits
3 and 6: 0 hits
1 and 7: 0 additional relevant hits of 2 hits
2and 7: 0 hits
3 and 7: 0 hits

4b. Other sources

Google Scholar 5/22/11
Limits: "Search articles only in the following subject areas: Medicine, Pharmacology and Veterinary Science"
1 and 4, 5, 6 or 7: 1 additional relevant hit (examined first 1000 of 20,200)
2 and 4, 5, 6 or 7: no additional relevant hits (examined first 1000 of 115,000)
3 and 4, 5, 6 or 7: no additional relevant hits (examined first 1000 of 81,300)

-In addition all references of identified articles and in particular the references of the following relevant review articles were checked:
(Levy 1998), (Morley 2011), (Plunkett 2008) and the AHA ALS-D-029A worksheet, yielding an additional 12 references.

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

Inclusion criteria

Use of bicarbonate in CPCR.

Exclusion criteria

Pediatric and neonatal studies. Not true cardiac arrest models (i.e. exsanguination without cardiac arrest). Abstracts only. Editorials.

4d. Number of articles/sources meeting criteria for further review: 59

Target Species
14 relevant RCTs were identified in dogs
5 relevant blinded RCTs were identified in dogs
0 relevant clinical studies were identified in target species

Non-target Species
2 blinded RCTs in humans were identified in humans
8 prospective cohort studies were identified in humans
6 retrospective studies were identified in humans

8 RCTs were identified in swine
1 observational study was identified in swine

5 RCTs were identified in rats

1 meta-analysis was identified (multiple species)

5. Summary of evidence

Evidence Supporting Clinical Question

Good			Bar-Joseph 1998; A Eleff 1995; E=cerebral pH Leong 2001; A Vukmir 1995; A			*Katz 2002; A* *Liu 2002; A, E=cerebral perfusion pressure* *Sun 1996; E=LV function* *Vukmir 2006; B*
Fair			Redding 1968; A Sanders 1990; A			*Stiehl 1995; A*
Poor			Ledingham 1962; E=pH, pCO2, BE, HCO3, neuro status, arrhythmia			*Bar-Joseph 2005; A,D* *Kirimli 1969; A*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation endpoint
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other
Italics = *Non-target species studies*

Evidence Neutral to Clinical question

Good			Blecic 1991; A *Neumar 1995; A* Sanders 1988; E=cerebral pH, pCO2			*Dybvik 1995; C* *Federiuk 1991; A* *Gazmuri 1990; A, E=coronary venous pCO2* *Gedebord 1989; E=epi response* *Kette 1990; A, E=myocardial pH* *Lathers 1989; E=MAP, circulating catecholamines* *Reynolds 2007; E= time to first drug* *Rubertsson 1993; E=MAP, PAP* *Walraven 1998; A, C*
Fair			Andersen 1967; E=PAP, MAP, CO Minuck 1977; A			*Androgue 1989; E=pH, pCO2* *Herlitz 1994; B,C* *Herlitz 1995; B,C* *Makine 2005; E=acid/base status* *von Planta 1989; E=myocardial pH, CO2*
Poor			Rosenberg 1989; E= cerebral pH			*Aufderheide 1992; E= hypernatremia, alkalemia* *Bar-Joseph 2002; E= time to administration* *Martinez 1995; E=pH*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation endpoint
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other
Italics = Non-target species studies

Evidence Opposing Clinical Question

Good			Berenyi 1975; E=CSF pH Bleske 1992; E=venous and arterial pH			*Kette 1991; A, E=CPP* *Sun 1999; B, E=CPP, LV function*

			Bleske 1994 E=pCO2, pH) Bleske 1995; E=CPP, MAP after epi Guerci 1986; A			*Wiklund 1986; E=cerebral pCO2 Wiklund 1990; A Wiklund 1997; E=myocardial metabolites*
Fair			Bishop 1976; E=serum osmolality			*Suljaga-Pechtel 1984; A Delooz 1989; C,D*
Poor						*Geraci 2009; E=alkalemia Roberts 1990; C Weil 1985; B*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation endpoint
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other
Italics = Non-target species studies

6. Reviewer's Final Comments

Discussion:
Concern over the possible detrimental effects of iatrogenic increases in serum osmolality, alkalemia, and paradoxic cerebral and myocardial acidosis as well as a lack of consensus for clinical benefit in humans have results in the recommendation against the routine use of exogenous buffers in human CPR (AHA 2010 consensus guidelines). Increases in serum osmolality after sodium bicarbonate administration have been documented in canine experimental models of CPR (Bishop 1976). Venous and arterial alkalemia have also been reported in canine experimental models of CPR (Bleske 1992, 1994). Studies on cerebral pH and CO2 concentrations in canine models are conflicting. Berenyi (1975) showed a decrease in cerebral pH in dogs receiving sodium bicarbonate, while several other studies have shown neutral to positive effects on cerebral pH after bicarbonate administration (Sanders 1988, Eleff 1995, Rosenberg 1989).

Justifications for the use of sodium bicarbonate have included theoretical improvement in catecholamine responsiveness with correction of acidemia, however experimental studies in dogs and rats suggest that administration of exogenous buffer does not improve cardiovascular response to catecholamine administration (Gedeborg 1989, Bleske 1995, Anderson 1967).

Two prospective observational studies (LOE 6, fair) in humans documented decreased survival when buffer was administered during CPR (Delooz 1989, Suljaga-Pechtel 1984), however six similar studies showed no effect on survival (vanWalraven 1998, Herlitz

1994, Herlitz 1995, Makino 2005, Adrogue 1989), and one study showed a slight increase in ROSC with bicarbonate administration (Stiell 1995).

One retrospective human study (LOE 6, poor quality) showed increased in-hospital mortality with the administration of bicarbonate during CPR, while another showed a slight increase in ROSC when bicarbonate was administered (Bar-Joseph 2005).

Clinical studies in dogs and cats are lacking, however several experimental studies in canine models of CPR (LOE 3) appear to show improved ROSC with buffer administration (Kirimli 1969, Leong 2001, Redding 1968, Sanders 1990, Vukmir 1995, Bar-Joseph 1998). In addition, Ledingham (1962) showed fewer post-ROSC arrhythmias in dogs receiving bicarbonate during resuscitation. Of these studies, Leong, Sanders, Vukmir and Bar-Joseph received good quality ratings. The Kirimli study lacked appropriate statistical analysis and included dogs that were crossed over within 30 minutes of completing each arm of the experiment. The Redding study received a fair rating due to the variation introduced by lack of dose scaling to weight of the experimental animals and lack of blinding. The Ledingham study was also problematic in its lack of appropriate statistic analysis and the dependency of the treatment group bicarbonate doses on the control group acid-base status.

In contrast, Blecic (1991) and Guerci (1986) are two good quality LOE 3 studies that failed to show improved ROSC with buffer administration.

Two high quality randomized controlled studies in humans (LOE 6) have shown conflicting results, with Dybvik (1995) showing no improvement in survival to hospital discharge with the use of tribonat compared to saline, and Vukmir (2006) showing a trend (P=0.007) towards improved survival with bicarbonate administration in prolonged arrest (>15min).

Outcome studies in swine (LOE 6) are similarly conflicted, with three good quality RCTs failing to show improvement in ROSC with buffer administration (Federiuk 1991, Gazmuri 1990, Kette 1990), one good-quality study showing a decrease in ROSC with bicarbonate administration compared to saline (Kette 1991), and one good-quality study showing improved ROSC with tribonat or bicarbonate administration compared to saline (Liu 2002).

Similar studies in rats are also contradictory, with good-quality studies showing both improved ROSC with carbicarb administration (Katz 2002) and decreased survival and coronary perfusion pressure with the administration of tromethamine or bicarbonate (Sun 1999).

In summary, the lack of consensus in experimental studies in dogs, the lack of clinical studies in species of interest, and the potential for harm preclude the recommendation for routine use of buffers in canine or feline CPR. The canine experimental studies that appear to show a benefit to buffer administration highlight the need for high-quality clinical studies in this species.

Conclusion:
Consensus on Science:
Evidence from four high-quality LOE 3 studies in dogs [4, 31, 43,5 2], in addition to three high-quality studies in non-target species (LOE 6)[25, 32, 53], show improved survival when buffer is administered during CPR. In contrast, two high-quality experimental studies in dogs [9, 21] and four high-quality studies in other species[15, 17, 18, 27] show no effect of buffer administration on survival. Although no canine studies showed a detrimental effect of buffer administration, two high-quality experimental studies in other species (LOE 6) showed decreased survival when buffer was administered during CPR[26, 49].

Treatment recommendation

Sodium bicarbonate should not be routinely administered during CPR, however it may be reasonable to consider in those patients undergoing prolonged CPR (>15 minutes).

8. Acknowledgements

The author wishes to thank Dr. Rush and Dr. Rozanski for their help and mentorship.

9. Citation list

1: Adrogué, H.J. et al., 1989. Assessing acid-base status in circulatory failure. Differences between arterial and central venous blood. *The New England journal of medicine*, 320(20), pp.1312-6.

To assess arteriovenous differences in acid-base status, we measured the pH and partial pressure of carbon dioxide (PCO2) in blood drawn simultaneously from the arterial and central venous circulations in 26 patients with normal cardiac output, 36 patients with moderate and 5 patients with severe circulatory failure, and 38 patients with cardiac or cardiorespiratory arrest. The patients with normal cardiac output had the expected arteriovenous differences: venous pH was lower by 0.03 unit, and venous PCO2 was higher by 0.8 kPa (5.7 mm Hg). These differences widened only slightly in those with moderate cardiac failure. Additional simultaneous determinations in mixed venous blood from pulmonary arterial catheters were nearly identical to those in central venous blood. In the five hypotensive patients with severe circulatory failure there were substantial differences between the mean arterial and central venous pH (7.31 vs. 7.21) and PCO2 (5.8 vs. 9.0 kPa [44 vs. 68 mm Hg]). Large arteriovenous differences were present during cardiac arrest in patients whose ventilation was mechanically sustained, whether sodium bicarbonate had been administered (pH, 7.27 vs. 7.07; PCO2, 5.8 vs. 8.6 kPa [44 vs. 65 mm Hg]) or not (pH, 7.36 vs. 7.01; PCO2, 3.7 vs. 10.2 kPa [28 vs. 76 mm Hg]). By contrast, in patients with cardiorespiratory arrest, large arteriovenous differences were noted only when sodium bicarbonate had been given (pH, 7.24 vs. 7.01; PCO2, 9.5 vs. 16.9 kPa [71 vs. 127 mm Hg]). We conclude that both arterial and central venous

blood samples are needed to assess acid-base status in patients with critical hemodynamic compromise. Although information about arterial blood gases is needed to assess pulmonary gas exchange, in the presence of severe hypoperfusion, the hypercapnia and acidemia at the level of the tissues are detected better in central venous blood.

1. Level of Evidence – 6 non-target species (human)
2. Methodological quality – fair – prospective observational
3. Magnitude of any observed effect – large
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral/NA
5. Outcome(s) assessed – E (venous and arterial pH and pCO2)
6. Relevance to the question asked – This article raises the issue of measurement of serum bicarbonate – significant differences between venous and arterial pH and PCO2 are present in patients with cardiorespiratory arrest that receive sodium bicarbonate and mechanically ventilated patients with cardiac arrest

2: Andersen, M.N., Border, J.R. & Mouritzen, C.V., 1967. Acidosis, catecholamines and cardiovascular dynamics: when does acidosis require correction? *Annals of surgery*, 166(3), pp.344-56.

1. Level of Evidence – 3 target species (canine)
2. Methodological quality – fair; RCT
3. Magnitude of any observed effect – mild (no change in epi responsiveness with decreasing pH until <6.8)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E (PAP, MAP, CO)
6. Relevance to the question asked – Respiratory acidosis induced with ventilation with CO2, metabolic acidosis induced with lactic acid infusion. Epinephrine's effects were only blunted at pH between 6.6-6.8

3: Aufderheide, T.P. et al., 1992. Prehospital bicarbonate use in cardiac arrest: a 3-year experience. *The American journal of emergency medicine*, 10(1), pp.4-7.

The American Heart Association no longer recommends the routine use of sodium bicarbonate in cardiac arrests. Reasons cited include the lack of documented effect on clinical outcome and potential adverse effects of metabolic alkalosis and hypernatremia. We reviewed 36 months of experience with 619 nontrauma adult, prehospital cardiac arrest patients to identify 273 successful resuscitations who had emergency department blood gases and electrolytes performed. Determination of complications associated with prehospital intravenous sodium bicarbonate and its impact on survival in resuscitated patients was undertaken. Fifty-eight patients did not receive sodium bicarbonate (NO

HCO3 group) and had short cardiopulmonary resuscitation (CPR) times (7.4 +/- 5.5 minutes). Two hundred fifteen patients did receive sodium bicarbonate (HCO3 group) and had significantly longer CPR times (23.3 +/- 13.5 minutes, P less than or equal to .001). Both groups demonstrated routine early chest compression and hyperventilation as evidenced by no significant difference in paramedic response time or rate of intubations. Initial emergency department blood gas results of both groups were not significantly different. No patients in the NO HCO3 group had hypernatremia (sodium [Na]+ greater than 150), whereas four patients (2%) in the HCO3 group were hypernatremic. Eight patients (14%) in the NO HCO3 group and 37 patients (17%) in the HCO3 group were alkalotic with pH values greater than 7.49 (P = NS). Six patients (10%) of the NO HCO3 group and 24 patients (11%) of the HCO3 group had a metabolic component to the alkalosis as defined by a positive base excess value (P = NS).

1. Level of Evidence – 6 (retrospective in a non-target species)
2. Methodological quality – poor
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – Neutral
5. Outcome(s) assessed – E = hypernatremia, alkalemia
6. Relevance to the question asked – 2% incidence of hypernatremia in successfully resuscitated patients that received bicarb compared to 0 that did not, 17% incidence of alkalemia with bicarb, 14% without (not significant)

4: Bar-Joseph, G. et al., 2005. Improved resuscitation outcome in emergency medical systems with increased usage of sodium bicarbonate during cardiopulmonary resuscitation. *Acta anaesthesiologica Scandinavica*, 49(1), pp.6-15.

Background: The use of sodium bicarbonate (SB) in cardio- pulmonary resuscitation (CPR) is controversial. This study analyzes the effects of SB use on CPR outcome in the Brain Resuscitation Clinical Trial III (BRCT III), which was a multicenter randomized trial comparing high-dose to standard-dose epinephrine during CPR. Sodium bicarbonate use in BRCT III was optional.

Methods: The entire BRCT III database was reviewed. Analy- sis included only patients who arrested out of the hospital and whose time from collapse to initiation of ACLS was no longer than 30 min (total n 1⁄4 2122 patients). Sodium bicarbonate use by the 16 participating study sites was analyzed. The study sites were divided according to their SB usage profile: 'low SB user' sites administered SB in less than 50% of CPRs and their first epinephrine to SB time exceeded 10min; and 'high SB user' sites used SB in over 50% of CPRs and their first epi- nephrine to SB time was <10 min.

Results: Sites' SB usage rates ranged between 3.1% and 98.2% of CPRs. Sodium bicarbonate usage rates correlated inversely with the sites' intervals from collapse

(r1⁄4 0.579 P1⁄40.018) from initiation of ACLS (r1⁄4 0.685 P1⁄40.003) and from first epinephrine (r 1⁄4 0.611 P 1⁄4 0.012) to SB administration.

Mean ROSC rate in the 'high SB user' sites was 33.5% (CI 1⁄4 30.0—37.0) compared to 25.7% (CI 1⁄4 23.1—28.4) in the 'low SB user' sites. In the 'high SB user' sites, hospital discharge rate was 5.3% (CI 1⁄4 3.6—7.0) compared to 3% (CI 1⁄4 2.0—4.0) in the 'low SB user' sites, and 5.3% (CI 1⁄4 3.6—7.0) had a favorable neurological outcome compared to 2.1% (CI 1⁄4 1.2—3.0) in the 'low SB user' sites. Collapse to ACLS interval was 8.5min (CI 1⁄4 8.1—9.0) in the 'high SB user' sites compared to 10.2 min (CI 1⁄4 9.8—10.6) in the 'low SB user' sites, and their ACLS to first epinephrine interval was 7.0 min (CI 1⁄4 6.5—7.5) compared to 9.7 min (CI 1⁄4 9.3—10.2). Multivariate regression analysis found that belonging to 'high SB user' sites independently increased the chances for ROSC (OR 1.36, CI 1.08—1.7) and for achieving a good neurological outcome (OR 2.18, CI 1.23—3.86).

Conclusions: Earlier and more frequent use of SB was associated with higher early resuscitation rates and with better long-term outcome. Sodium bicarbonate may be beneficial during CPR, and it should be subjected to a randomized clinical trial.

1. Level of Evidence – 6 non-target species (human)
2. Methodological quality – poor; related rates of ROSC, neurologic outcome to rate of bicarbonate use at site
3. Magnitude of any observed effect – modest
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supports
5. Outcome(s) assessed – A,D
6. Relevance to the question asked – limited by poor study design, but improved ROSC and neurologic recovery at "high-SB sites"

4: Bar-Joseph, G. et al., 1998. Comparison of sodium bicarbonate, Carbicarb, and THAM during cardiopulmonary resuscitation in dogs. *Critical care medicine*, 26(8), pp.1397-408.

OBJECTIVES: During cardiopulmonary resuscitation (CPR), elimination of CO2 was shown to be limited by low tissue perfusion, especially when very low perfusion pressures were generated. It has therefore been suggested that sodium bicarbonate (NaHCO3), by producing CO2, might aggravate the hypercarbic component of the existing acidosis and thereby worsen CPR outcome. The objectives of this study were to evaluate the effects of CO2 producing and non-CO2 producing buffers in a canine model of prolonged ventricular fibrillation followed by effective CPR.
DESIGN: Prospective, randomized, controlled, blinded trial.
SETTING: Experimental animal research laboratory in a university research center.
SUBJECTS: Thirty-eight adult dogs, weighing 20 to 35 kg.

INTERVENTIONS: Animals were prepared for study with thiopental followed by halothane, diazepam, and pancuronium. Ventricular fibrillation was electrically induced, and after 10 mins, CPR was initiated, including ventilation with an FIO2 of 1.0, manual chest compressions, administration of epinephrine (0.1 mg/kg every 5 mins), and defibrillation. A dose of buffer, equivalent to 1 mmol/kg of NaHCO3, was administered every 10 mins from start of CPR. Animals were randomized to receive either NaHCO3, Carbicarb, THAM, or 0.9% sodium chloride (NaCl). CPR was continued for up to 40 mins or until return of spontaneous circulation.
MEASUREMENTS AND MAIN RESULTS: Buffer-treated animals had a higher resuscitability rate compared with NaCl controls. Spontaneous circulation returned earlier and at a significantly higher rate after NaHCO3 (in seven of nine dogs), and after Carbicarb (six of ten dogs) compared with NaCl controls (two of ten dogs). Spontaneous circulation was achieved twice as fast after NaHCO3 compared with NaCl (14.6 vs. 28 mins, respectively). Hydrogen ion (H+) concentration and base excess, obtained 2 mins after the first buffer dose, were the best predictors of resuscitability. Arterial and mixed venous Pco2 did not increase after NaHCO3 or Carbicarb compared with NaCl.
CONCLUSIONS: Buffer therapy promotes successful resuscitation after prolonged cardiac arrest, regardless of coronary perfusion pressure. NaHCO3, and to a lesser degree, Carbicarb, are beneficial in promoting early return of spontaneous circulation. When epinephrine is used to promote tissue perfusion, there is no evidence for hypercarbic venous acidosis associated with the use of these CO2 generating buffers.

1. Level of Evidence – 3 target species (dog)
2. Methodological quality – good
3. Magnitude of any observed effect – Marked increase in ROSC (buffer 18/20 v. no buffer 2/10, $P<0.05$), faster ROSC with buffer
   -not truly blinded for THAM (lg. volume)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – support
5. Outcome(s) assessed – A
6. Relevance to the question asked – Canine experimental model of ventricular fibrillation. CPR started after 10 min of fibrillation, low-dose epi given (0.1mg/kg) after start of CPR, increased ROSC compared to saline with either buffer.

6: Bar-Joseph, G. et al., 2002. Clinical use of sodium bicarbonate during cardiopulmonary resuscitation--is it used sensibly? *Resuscitation*, 54(1), pp.47-55.

This study retrospectively analyzed the pattern of sodium bicarbonate (SB) use during cardiopulmonary resuscitation (CPR) in the Brain Resuscitation Clinical Trial III (BRCT III). BRCT III was a prospective clinical trial, which compared high-dose to standard-dose epinephrine during CPR. SB use was left optional in the study protocol. Records of 2915 patients were reviewed. Percentage, timing and dosage of SB administration were correlated with demographic and cardiac arrest variables and with times from collapse to Basic Life Support, to Advanced Cardiac Life Support (ACLS) and to the major interventions performed during CPR. SB was administered in 54.5% of the resuscitations. The rate of SB use decreased with increasing patient age-primarily reflecting shorter CPR

attempts. Mean time intervals from arrest, from start of ACLS and from first epinephrine to administration of the first SB were 29+/-16, 19+/-13, and 10.8+/-11.1 min, respectively. No correlation was found between the rate of SB use and the pre-ACLS hypoxia times. On the other hand, a direct linear correlation was found between the rate of SB use and the duration of ACLS. We conclude that when SB was used, the time from initiation of ACLS to administration of its first dose was long and severe metabolic acidosis probably already existed at this point. Therefore, if SB is used, earlier administration may be considered. Contrary to physiological rationale, clinical decisions regarding SB use did not seem to take into consideration the duration of pre-ACLS hypoxia times. We suggest that guidelines for SB use during CPR should emphasize the importance of pre-ACLS hypoxia time in contributing to metabolic acidosis and should be more specific in defining the duration of "protracted CPR or long resuscitative efforts", the most frequent indication for SB administration.

1. Level of Evidence - 6 non-target species (human)
2. Methodological quality – poor (post-hoc retrospective analysis of brain resuscitation database in non-target species)
3. Magnitude of any observed effect – none?
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E= time to bicarbonate administration
6. Relevance to the question asked – Measured time to bicarbonate administration.

Authors argue excessively delayed and that delayed administration interferes with the beneficial effects of bicarb as pre-CPR hypoxemia and severe acidosis is *likely* to exist

7: Berenyi, K.J., Wolk, M. & Killip, T., 1975. Cerebrospinal fluid acidosis complicating therapy of experimental cardiopulmonary arrest. *Circulation*, 52(2), pp.319-24.

Cardiopulmonary resuscitation (CPR) may be followed by slow recovery of brain function. The possible role of bicarbonate therapy was assessed by analysis of arterial blood and cerebrospinal fluid (CSF) in 20 dogs during cardiac arrest and CPR. Samples were taken in the control period and every 5 minutes post-arrest of 20 minutes. Group I received no post-arrest CPR. Arterial pH fell from 7.37 to 7.31 (P less than 0.01) and CSF pH from 7.34 to 6.94 (P less than 0.001). Arterial pCO2 rose from 39 to 65 mm Hg (P less than 0.005) and CSF pCO2 increased from 47 to 123 (P less than 0.02). With CPR alone (group II) arterial pH decreased from 7.39 to 7.19 (P less than 0.005), while arterial pCO2 and CSF pH and pCO2 were undhanged. CPR with bicarbonate therapy (mEq = weight in kg times 0.43 times 1.1 mEq/min of arrest) given every 5 minutes (group III), resulted in a rise in arterial pH from 7.41 to 7.81 (P less than 0.02). Excess bicarbonate administration during CPR may result in a marked dissociation between arterial and CSF pH as a consequence of rapid CO2 diffusion across the blood-brain barrier. Large ampounts of NaHCO3 given during CPR may contribute to post-CPR cerebral depresssion.

1. Level of Evidence – 3 target species (dog)
2. Methodological quality – good (RCT, not blinded)

3. Magnitude of any observed effect – marked – CSF pH as low as 7.18 in bicarb group (P>0.005)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – Opposing
5. Outcome(s) assessed – E- CSF and arterial pH
6. Relevance to the question asked – No bicarb CPR had relatively stable CSF pH. Although bicarb prevented arterial acidosis, CSF pH dropped markedly. (gave BW(kg)x0.43x1.1mEq bicarb/min arrest @5,10,15 and 20 min)

8: Bishop, R.L. & Weisfeldt, M.L., 1976. Sodium bicarbonate administration during cardiac arrest. Effect on arterial pH PCO2, and osmolality. *JAMA : the journal of the American Medical Association*, 235(5), pp.506-9.

Arterial pH, Pco2, and osmolality were determined serially during cardiac resuscitation in patients and in dogs, with and without administration of sodium bicarbonate. 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 Pco2, which parallels the rise in pH despite adequate ventilation; (3) during prolonged cardiac and resuscitation, there is a rise in arterial osmolality that is accentuated by sodium bicarbonate. 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. These studies also point to the need for a reappraisal of other buffers that do not elevate the arterial Pco2.

1. Level of Evidence – 3 target species (dog, also human)
2. Methodological quality – fair (not randomized but controlled)
3. Magnitude of any observed effect – marked increase in osmolality in treated group (330 @ 10min P<0.001); pCO2 also higher in txt group; pH adequately controlled by ventilation in non-bicarb group
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – Opposed
5. Outcome(s) assessed – E-serum osmolality
6. Relevance to the question asked – Canine experimental portion – treatment group received 1mEq/kg bicarb after 1 min resuscitation (3min apnea); human observational portion – little to no relevance

9: Blecic, S. et al., 1991. Correction of metabolic acidosis in experimental CPR: a comparative study of sodium bicarbonate, carbicarb, and dextrose. *Annals of emergency medicine*, 20(3), pp.235-8.

AB STUDY OBJECTIVE: Carbicarb, sodium bicarbonate, and 5% dextrose were compared for effects on resuscitability in a canine model of electromechanical

dissociation after ventricular fibrillation. DESIGN/INTERVENTIONS: 21 healthy mongrel dogs were anesthetized with pentobarbital, intubated, and mechanically supported. They were instrumented to measure heart rate, arterial pressure, pulmonary artery pressure, right atrial pressure, cardiac output, and arterial and mixed venous blood gases. The dogs were then subjected to a protocol that consisted of three successive CPR episodes. During each episode they were treated with repeated injections of one of the three substances, randomly chosen. After two minutes of ventricular fibrillation and four minutes of electromechanical dissociation, CPR was started with a thumper (rate, 60; duty cycle, 50%). If recovery was not obtained after five minutes of CPR, 1 mEq/kg carbicarb or sodium bicarbonate or 5 mL D5W was injected in the right atrium. Half the dose of the same substance was injected every five minutes thereafter; 1 mg epinephrine was also injected every five minutes until recovery. Hemodynamic and gasometric evaluations were performed five and 20 minutes after recovery. This later evaluation served as baseline for the next CPR episode. MEASUREMENTS AND MAIN RESULTS: The duration and success rates of CPR are similar in the three CPR groups. Hemodynamic parameters were also similar during recovery. Bicarbicarb and sodium bicarbonate increased bicarbonate levels and corrected pH in the arterial and mixed venous blood. There was no difference in the blood gas values after carbicarb and sodium bicarbonate. CONCLUSION: In this model of cardiac arrest, carbicarb was not superior to sodium bicarbonate in the correction of metabolic acidosis during CPR.

1. Level of Evidence – 3 target species (dog)
2. Methodological quality – good – Randomized crossover trial
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – A
6. Relevance to the question asked – 1mEq bicarb or carbicarb v. D5w after 5 min of CPR, repeat ½ dose 5 min, 1mg epi q5min

Bleske, B.E. et al., 1992. Effects of different dosages and modes of sodium bicarbonate administration during cardiopulmonary resuscitation. *The American journal of emergency medicine*, 10(6), pp.525-32.

Systemic acidosis occurs during cardiac arrest and cardiopulmonary resuscitation (CPR). The present study investigated the effect of different modes of sodium bicarbonate administration on blood gas parameters during CPR. Arterial and venous blood gases were obtained during 10 minutes of CPR which was preceded by 3 minutes of unassisted ventricular fibrillation in 36 dogs. Following 1 minute of CPR, the animals received one of four treatments in a randomized and blinded manner: normal saline (NS), sodium bicarbonate bolus dose 1 mEq/kg (B), sodium bicarbonate continuous infusion 0.1 mEq/kg/min (I), and sodium bicarbonate bolus dose (0.5 mEq/kg) plus continuous infusion 0.1 mEq/kg/min (L+I). Eleven dogs completed NS, 8 B, 8 I, and 9 L+I protocol. Following NS infusion, both arterial and venous pH declined consistently over time.

Significant differences compared with NS treatment in venous pH were observed at 12 minutes of ventricular fibrillation (L+I, 7.27 +/- 0.05; NS, 7.15 +/- 0.05; B, 7.20 +/- 0.05; I, 7.24 +/- 0.04, each bicarbonate treatment versus NS, and L+I versus B, (P < .05). The B group had an elevated venous PCO2 (mm Hg) concentration following 6 minutes of ventricular fibrillation compared with NS, L+I, and I groups (81 +/- 14 versus 69 +/- 10 versus 68 +/- 10 versus 71 +/- 8, respectively, (P = .07). Arterial pH and PCO2 values showed a similar trend as the venous data with the L+I group demonstrating arterial alkalosis (pH > 7.45) at 12 minutes of ventricular fibrillation.

1. Level of Evidence – 3 target species (dog)
2. Methodological quality – good – blinded RCT
3. Magnitude of any observed effect – modest
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposed
5. Outcome(s) assessed – E = arterial and venous pH
6. Relevance to the question asked – (1mEq/kg bolus v. 0.5mEq bolus + CRI 0.1mEq/kg/min v. CRI alone) all groups developed arterial alkalosis continuous infusion caused the least venous alkalosis.

11: Bleske, B.E., Rice, T.L. & Warren, E.W., 1994. An alternative sodium bicarbonate regimen during cardiac arrest and cardiopulmonary resuscitation in a canine model. *Pharmacotherapy*, 14(1), pp.95-9.

We evaluated the effect of frequent, early bolus administration of low-dose sodium bicarbonate (NaHCO3) on blood gas values during ventricular fibrillation and cardiopulmonary resuscitation (CPR) compared with normal saline and standard bolus doses of NaHCO3. This was a randomized laboratory investigation involving 13 mongrel dogs and 18 experiments (5 dogs were used in a crossover manner). Each dog underwent 3 minutes of ventricular fibrillation, followed by 15 minutes of CPR. Animals were randomly assigned to one of three treatments administered early in the resuscitation effort: NaHCO3 0.5 mEq/kg at 5, 10, and 15 minutes of ventricular fibrillation (SB); NaHCO3 1 mEq/kg at 5 minutes and 0.5 mEq/kg at 15 minutes of fibrillation (SB); or 0.9% NaCl 1 ml/kg at 5 minutes and 0.5 ml/kg at 15 minutes of fibrillation (P). A total of 15 experiments were included for analysis. Arterial and venous blood gases were sampled at 4, 8, 13, and 18 minutes of fibrillation. The SB group demonstrated the highest arterial partial pressures of carbon dioxide (pCO2) at each sampling point after NaHCO3, including the 18-minute sample: 42 +/- 12, 29 +/- 11, and 35 +/- 10 torr for SB, P, and B, respectively. In addition, SB produced arterial alkalemia (pH > 7.45) after NaHCO3 administration. The arterial pH at 18 minutes of fibrillation for SB, P, and B was 7.46 +/- 0.14, 7.29 +/- 0.07, and 7.41 +/- 0.1, respectively. Similar trends for pCO2 and pH were observed for venous samples.

1. Level of Evidence – 3 target species (dog)
2. Methodological quality – good – RCT, partial cross-over
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposed

5. Outcome(s) assessed – E = arterial, venous pCO2 and pH
6. Relevance to the question asked – (0.5mEq NaHCO3 at 5, 10, 15 min fibrillation v. 1mEq NaHCO3 at 5 min + 0.5mEqNaHCO3 at 15 min fibrillation v. saline) – early low dose and standard dose groups developed arterial alkalemia and trend toward hypercarbia; early group had highest pCO2 and alkalemia at end of CPR.

12: Bleske, B.E. et al., 1995. Effect of high-dose sodium bicarbonate on the vasopressor effects of epinephrine during cardiopulmonary resuscitation. *Pharmacotherapy*, 15(5), pp.660-4.

We attempted to determine the effect of extreme alkalemia induced by highdose sodium bicarbonate on the vasopressor effects of epinephrine during cardiopulmonary resuscitation (CPR). Subjects in this randomized, blinded study performed in a controlled laboratory environment were 12 mongrel dogs that had had a previous episode of CPR. Each dog underwent 3 minutes of ventricular fibrillation (VF) followed by 7 minutes of closed-chest CPR. Animals were assigned to receive either sodium bicarbonate 3 mEq/kg and epinephrine 0.1 mg/kg, or normal saline 3 ml/kg and epinephrine 0.1 mg/kg. The sodium bicarbonate or normal saline was infused over 2 minutes beginning at 4 minutes of VF (1 min of CPR) followed by bolus epinephrine. Arterial pH in the sodium bicarbonate group was significantly higher at each sampling point (7.7 +/- 0.1 vs 7.29 +/- 0.06 at 1 min after drug, $p < 0.001$). However, there were no statistically or clinically significant differences in coronary perfusion pressure between the groups at any time: 29 +/- 13 versus 32 +/- 21 mm Hg 1 minute, and 22 +/- 12 versus 26 +/- 19 mm Hg 4 minutes after epinephrine for sodium bicarbonate and normal saline, respectively ($p > 0.7$). Increased arterial pH (alkalemia) induced by high-dose sodium bicarbonate administration did not improve the vasopressor effects of epinephrine during CPR in this canine model. These results suggest the limited value of administering sodium bicarbonate during CPR to improve the responsiveness to epinephrine.

1. Level of Evidence – 3
2. Methodological quality – good; blinded RCT
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposed
5. Outcome(s) assessed – E - CPP, MAP after epi
6. Relevance to the question asked – No improvement in epi responsiveness after 3mEq/kg bicarb (blinded with saline); dogs had previous arrest in other study

13: Cervantes, M. et al., Temporal course of metabolic acidosis during cardiorespiratory arrest in cats. Treatment with sodium bicarbonate. *Archivos de investigación médica*, 17(1), pp.1-10.

1. Level of Evidence – 3* unable to locate, no abstract, target species (cats)

2. Methodological quality –
3. Magnitude of any observed effect –
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed –
5. Outcome(s) assessed –
6. Relevance to the question asked –

14: Delooz, H.H. & Lewi, P.J., 1989. Are inter-center differences in EMS-management and sodiumac-bicarbonate administration important for the outcome of CPR? The Cerebral Resuscitation Study Group. *Resuscitation*, 17 Suppl, pp.S161-72; discussion S199-206.

The hospital of Brugge relies on selection of the emergency calls and sends a Mobile Intensive Care Unit (MICU) whenever cardiac arrest (CA) is suspected. The University Hospital of Leuven does no selection of calls and responds to every emergency call by sending an ambulance with an advanced life support (ALS) trained nurse. The MICU is called when the ambulance crew recognizes the emergency to be a CA. The Leuven system is a so-called tiered system. Although MICU-response times are significantly longer in Leuven than in Brugge, no difference is found as to the success of CPCR. The immediate response to all emergency calls by specialized E.D. nurses (paramedic) capable of ALS, seems to make up for the difference in MICU-response times. The University Hospital of Jette has a higher success-rate for CPCR for in-hospital CA, than the University Hospitals of Leuven. Due to size and lay-out differences, the MICU-response times are shorter in Jette than in Leuven. Basic life support (BLS) provided by doctors and nurses present at the scene, does not seem to be able to compensate for longer MICU-arrival times. The introduction of semi-automatic or automatic defibrillators, to be used by the BLS trained medical and nursing personnel, might be able to make up for the longer MICU-intervention times. Inter-center differences were witnessed as far as the amount of sodium-bicarbonate infused during CPR. Within each group of total duration of CPR an inverse correlation exists between the amount of bicarbonate infused and the success rate of CPCR. Partial correlation between the bicarbonate infused and the survival with regaining of consciousness at 14 days post-CPR, with constant CPR-time, is statistically significant. This indicates that long-term CPCR success is inversely correlated with increasing amounts of sodium-bicarbonate infused. Short duration of CPR and low adrenaline dosage correlate with immediate and long-term success of CPR. On the contrary, low versus high bicarbonate dosage has hardly any influence on immediate success (restoration of spontaneous circulatory activity) but low bicarbonate dosage favours long-term success (survival accompanied by recuperation of brain function). Our data support a negative effect on long-term survival with recuperation of consciousness from infusion of more than 1 mEq/kg body weight of sodium-bicarbonate during CPR. No final conclusions can be drawn so far as to the mechanisms of this negative effect at the level of the brain.
1. Level of Evidence – 6* unable to access, unclear study design; non-target species (human)
2. Methodological quality – poor (retrospective, non-target species)

3. Magnitude of any observed effect – significant
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – Opposing
5. Outcome(s) assessed – C, D
6. Relevance to the question asked – amount of bicarb infused during long CPR inversely correlated with intact neurologic survival; bicarb >1mEq negative effect on long-term neurologically intact survival

15: Dybvik, T., Strand, T. & Steen, P.A., 1995. Buffer therapy during out-of-hospital cardiopulmonary resuscitation. *Resuscitation*, 29(2), pp.89-95.

The effects of infusing a buffer solution on resuscitability and outcome was tested in patients during out-of-hospital cardiac arrest. A number (502) of adults with asystole or ventricular fibrillation with failure of first defibrillation attempt were entered into a prospective, randomized, double-blind, controlled trial. Of these, 245 patients received 250 ml of sodium bicarbonate-trometamol- phosphate mixture with buffering capacity 500 mmol/l and 257 patients received 250 ml 0.9% saline. Except for the investigational infusion, all patients were resuscitated according to international guidelines. Eighty-seven patients (36%) receiving buffer were admitted to hospital ICU and 24 (10%) were discharged from hospital alive, vs. 92 (36%) and 35 (14%) receiving saline (95% confidence interval (CI) for difference between groups: -6%-6% for rate of admission and -1%-9% for rate of discharge). Using a logistic regression analysis, ventricular fibrillation as initial rhythm (odds ratio 8.06, CI 3.70-17.56) improved the outcome, whereas buffer therapy had no effect (odds ratio 0.77, CI 0.43-1.41). Mean base excess at hospital admission was -9 after Tribonat vs. -11 after saline (P = 0.04, CI for difference 0.2-3.8). Only 16 of the 502 patients had arterial alkalosis on arrival in the hospital and no patient had a positive base excess. Patients resuscitated after out-of-hospital cardiac arrest had metabolic acidosis, but buffer therapy did not improve the outcome.
1. Level of Evidence – 6
2. Methodological quality – good (RCT, non-target species)
3. Magnitude of any observed effect – no effect
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – C
6. Relevance to the question asked – Tribonat buffer v. saline out of hospital arrest - no effect on survival

16: Eleff, S.M. et al., 1995. Acidemia and brain pH during prolonged cardiopulmonary resuscitation in dogs. *Stroke; a journal of cerebral circulation*, 26(6), pp.1028-34.

AB BACKGROUND AND PURPOSE: Cardiopulmonary resuscitation (CPR) generating low perfusion pressures and beginning immediately after cardiac arrest maintains cerebral ATP but not cerebral pH or arterial pH. We tested the hypothesis that preventing severe arterial acidemia prevents cerebral acidosis, whereas augmenting arterial acidemia

augments cerebral acidosis. METHODS: In dogs anesthetized with pentobarbital and fentanyl, cerebral pH and ATP were measured with 31P MR spectroscopy and blood flow was measured with radiolabeled microspheres. A pneumatically controlled vest was placed around the thorax, and chest compressions were begun immediately after electrically induced cardiac arrest. Cerebral perfusion pressure was maintained with epinephrine at 30 mm Hg for 90 minutes. The arterial acidemia observed during CPR was untreated in a control group, corrected to a pH of 7.3 with the use of sodium bicarbonate, or maintained below pH 6.5 with intravenous lactic acid after 14 minutes of CPR. RESULTS: At 10 minutes of CPR, cerebral ATP (99 +/- 1.5%, control), blood flow (35 +/- 3 mL/min per 100 g), O2 consumption (4.0 +/- 0.2 mL/min per 100 g), and cerebral pH (7.05 +/- .03) were unchanged from prearrest values (mean +/- SEM). After 10 minutes of CPR in the control group, cerebral pH progressively fell (6.43 +/- 0.10 at 90 minutes) in parallel with cerebral venous pH. In the bicarbonate group cerebral pH was maintained higher (6.91 +/- 0.08). Cerebral blood flow, O2 consumption, and ATP were sustained near prearrest values in both groups. In the lactate group, however, the rate of decrease of cerebral pH was augmented (6.47 +/- 0.06 by 30 minutes), and cerebral blood flow and metabolism were significantly reduced. CONCLUSIONS: Cerebral pH decreased in parallel with blood pH when resuscitation was started immediately upon arrest even when cerebral O2 consumption and blood flow were near normal. Although cerebral metabolism was near normal during the first hour of CPR, systemic bicarbonate administration ameliorated the cerebral acidosis. This finding indicates that the blood-brain pH gradient is important at the subnormal cerebral perfusion pressures seen in CPR.

1. Level of Evidence – 3 target species (dog)
2. Methodological quality – good (non-blinded RCT)
3. Magnitude of any observed effect – modest
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supporting
5. Outcome(s) assessed – E-cerebral pH and energy metabolism
6. Relevance to the question asked – correction of arterial acidosis with bicarb also increased cerebral pH; cerebral ATP, blood flow and O2 metabolism comparable between control and bicarb, however group that received lactic acid had decreases in all 3

17: Federiuk, C.S. et al., 1991. The effect of bicarbonate on resuscitation from cardiac arrest. *Annals of emergency medicine*, 20(11), pp.1173-7.

Abstract STUDY OBJECTIVES: This study attempted to determine the effect of bicarbonate administration on resuscitation in a porcine model of prolonged cardiac arrest.
DESIGN: After instrumentation, 26 swine were subjected to ventricular fibrillation for 15 minutes (16 animals) or 20 minutes (ten animals) with no resuscitative efforts. INTERVENTIONS: Resuscitation attempts with open-chest cardiac massage and epinephrine were used in all animals after the arrest period. The experimental group was given sodium bicarbonate (3 mEq/kg), and the control group received 3% saline (5 mL/kg) at the initiation of cardiac massage.

MEASUREMENTS: Resuscitation success, hemodynamics, and arterial and mixed venous gases were compared in the bicarbonate and hypertonic saline-treated groups.
RESULTS: There was no difference in resuscitation rates between bicarbonate and nonbicarbonate-treated swine. After 15 minutes of ventricular fibrillation, six of eight bicarbonate-treated swine were resuscitated successfully compared with five of eight hypertonic saline-treated animals. None of the five bicarbonate-treated or five hypertonic saline-treated swine that underwent 20 minutes of ventricular fibrillation were resuscitated. The arterial and mixed venous pH values were significantly different in the bicarbonate-treated animals from values in the control group. There was no difference in systolic or diastolic blood pressures or myocardial perfusion pressure between the bicarbonate and hypertonic saline-treated animals.
CONCLUSION: Despite correlation of arterial and venous acidemia, the use of sodium bicarbonate did not improve resuscitation from prolonged cardiac arrest.

1. Level of Evidence – 6 prospective, non-target species (swine)
2. Methodological quality – good (experimental, non-target species - swine)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – Neutral
5. Outcome(s) assessed – A
6. Relevance to the question asked – Administration of 3mEq/kg bicarb after 15 min of v-fib did not improve ROSC compared to saline

18: Gazmuri, R.J. et al., 1990. Cardiac effects of carbon dioxide-consuming and carbon dioxide-generating buffers during cardiopulmonary resuscitation. *Journal of the American College of Cardiology*, 15(2), pp.482-90.

Recent studies have demonstrated an increase in carbon dioxide (CO2) tension (PCO2) in both mixed venous and coronary vein blood early in the course of cardiac arrest and cardiopulmonary resuscitation. Because increased PCO2 in the myocardium correlates with both ischemic injury and depression of contractile function, the effects of hypertonic solutions of either the CO2-"generating" sodium bicarbonate (NaHCO3) buffer, a mixture of sodium carbonate (Na2CO3) and sodium bicarbonate (carbicarb) acting as a CO2-"consuming" buffer, or saline placebo (NaCl) were compared during cardiopulmonary resuscitation in 25 healthy minipigs. Both buffer agents significantly increased the pH and HCO3- of arterial, mixed venous and coronary vein blood. Bicarbonate increased whereas carbicarb reduced blood PCO2 in the systemic circuit as anticipated. However, neither the PCO2 nor the lactate content of coronary vein blood was favorably altered by buffer therapy. Four of eight animals treated with bicarbonate, five of eight treated with carbicarb and six of nine placebo-treated animals were successfully resuscitated and had a comparable 24 h survival rate. Coronary perfusion pressure during precordial compression, a critical determinant of resuscitability, was transiently decreased by each of the hypertonic solutions. Accordingly, neither CO2-generating nor CO2-consuming buffers mitigated increases in coronary vein PCO2 or improved the outcome of cardiopulmonary resuscitation under these experimental conditions.

1. Level of Evidence – 6 non-target species (swine)
2. Methodological quality – good (RCT)
3. Magnitude of any observed effect – none to slight
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – A, E-coronary vein pCO2
6. Relevance to the question asked - neither bicarb or carbicarb mitigated increases in coronary vein PCO2 or improved the outcome of cardiopulmonary resuscitation under these experimental conditions.

19: Gedeborg, R. & Wiklund, L., 1989. The biological activity of adrenaline after injection through an intravenous cannula containing alkaline buffer. *Resuscitation*, 18(1), pp.49-58.

Since it is known that alkaline pH inactivates adrenaline it has been recommended that this drug not be administered in the same i.v. line as alkaline buffer solutions during cardiopulmonary resuscitation. In order to test the validity of this statement a simulation model of the clinical situation was designed where the biological activity of adrenaline was measured in anesthetized rats after having been mixed with alkaline buffer solution contained in a standard i.v. cannula. The biological activity of adrenaline was measured by comparing the blood pressure response after repeated administration of a test (adrenaline + alkaline buffer) and control (adrenaline + normal saline) solution to a rat which had previously received a ganglion-blocking agent. Two alkaline buffer solutions, sodium bicarbonate and Tris buffer mixture were tested. These resulted in a decrease of the biological effect of adrenaline to 77 +/- 6 and 82 +/- 9% of control values, respectively. If however, adrenaline mixed with Tris buffer mixture was injected into a recipient of phosphate buffer (pH 7.40 and buffer capacity equal to human blood) as much as 94 +/- 17% of its activity remained. The results lead us to suggest that, in the cardiopulmonary resuscitation situation, adrenaline may well be given via a cannula containing alkaline buffer solution without significant interference with its effect.
1. Level of Evidence – 6
2. Methodological quality – good (RCT), non-target species (rat)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E- epi response
6. Relevance to the question asked - minimal (77%-82% activity) to no effect (if recipient given buffer equivalent to human blood buffer capacity) on epi response if combined with buffer in infusion cannula

20: Geraci, M.J. et al., 2009. Prevalence of sodium bicarbonate-induced alkalemia in cardiopulmonary arrest patients. *The Annals of pharmacotherapy*, 43(7), pp.1245-50.

Abstract BACKGROUND: Intravenous sodium bicarbonate (SB) administration during cardiopulmonary arrest (CPA) is intended to counteract lactic acidosis due to hypoxia, poor perfusion, and anaerobic metabolism. Despite a lack of documented efficacy and a level III recommendation from the American Heart Association, SB is widely used during resuscitation events. SB has both theoretical and measurable adverse effects. Excess or poorly timed administration during a CPA may elevate a patient's pH, inducing alkalemia. Despite decades of controversy surrounding use of this drug, the prevalence of SB-induced alkalemia has not been previously documented.
OBJECTIVE: To estimate the prevalence of SB-induced alkalemia in inpatients after CPA and to investigate the pattern of SB administration.
METHODS: Medical records were retrospectively reviewed with attention to SB administration and arterial blood gas (ABG) data. After application of inclusion and exclusion criteria to 264 CPA patients, the study group comprised 88 patients. When measured, if PCO(2) and pH were above normal limits after SB administration, we concluded that SB contributed to the alkalemia.
RESULTS: Twenty-seven (31%) patients received SB without any ABG data, and 70 (79%) patients received at least one empiric SB dose. Of the 61 patients with ABG data, alkalemia occurred in 10, a prevalence of 16%. Administration of SB increased pH in only 9 (15%) other CPA patients and had no effect in the 42 (69%) remaining patients.
CONCLUSIONS: Administration of SB during CPA was causally linked with inducing alkalemia in 16% of patients. Early collection of ABG samples may assist in optimizing pH during CPA and thus reduce unwarranted empiric use of SB.

1. Level of Evidence – 6 non-target species (human)
2. Methodological quality – poor (retrospective, only 61 patients)
3. Magnitude of any observed effect – 16% prevalence
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposing
5. Outcome(s) assessed – E=alkalemia
6. Relevance to the question asked - 16% incidence of alkalemia in human in-patients given bicarb during CPR

21: Guerci, A.D. et al., 1986. Failure of sodium bicarbonate to improve resuscitation from ventricular fibrillation in dogs. *Circulation*, 74(6 Pt 2), pp.IV75-9.

To determine the value of sodium bicarbonate in resuscitation from ventricular fibrillation and the prevention of spontaneous refibrillation, sodium bicarbonate (1 meq/kg) or placebo was administered on a random basis to 16 pentobarbital-anesthetized dogs 18 min after the induction of ventricular fibrillation and cardiopulmonary resuscitation. Defibrillation was attempted 2 min after the administration of bicarbonate or placebo. All animals were successfully defibrillated, but three of eight bicarbonate-treated and two of eight control animals died in electromechanical dissociation (p = NS). Spontaneous refibrillation occurred in three animals in each group (p = NS). Successful resuscitation was not dependent on treatment, arterial or mixed venous Pco2, or arterial or mixed venous pH but correlated strongly with coronary perfusion pressure (p less than

.003). Spontaneous refibrillation occurred without relation to any identifiable variable. The gradient between diastolic aortic and right atrial pressures was 24 +/- 2 mm Hg in controls and 23 +/- 2 mm Hg in treated animals over the entire 20 min of cardiopulmonary resuscitation (p = NS). However, among animals successfully resuscitated, mean diastolic coronary perfusion pressure averaged 27 +/- 2 mm Hg compared with 20 +/- 1 mm Hg among those dying in electromechanical dissociation (p less than .02). For the final 2 min of resuscitation, after drug administration, these gradients were 31 +/- 2 and 23 +/- 2 mm Hg, respectively (p less than .01). Microsphere determined myocardial perfusion correlated with the diastolic aortic-right atrial perfusion pressure gradient (r = .86) and was 0.43 +/- 0.03 ml/min/g in survivors and 0.22 +/- 0.01 ml/min/g in nonsurvivors (p less than .01).

1. Level of Evidence – 3 target species - dog
2. Methodological quality – good
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral (no harm but no benefit)
5. Outcome(s) assessed – A
6. Relevance to the question asked - no improvement in ROSC with 1mEq/kg bicarb compared to placebo after 18 min fibrillation before defibrillation.

22: Heilbrunn, A. & Zimmerman, J.M., 1967. Cardiac arrest. The use of drugs in resuscitation. An experimental study. *The Journal of the Kansas Medical Society*, 68(8), pp.344-9.

1. Level of Evidence – * unable to access, no abstract avail
2. Methodological quality –
3. Magnitude of any observed effect –
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed –
5. Outcome(s) assessed –
6. Relevance to the question asked –

23: Herlitz, J. et al., 1994. Predictors of early and late survival after out-of-hospital cardiac arrest in which asystole was the first recorded arrhythmia on scene. *Resuscitation*, 28(1), pp.27-36.

AB BACKGROUND: A large proportion of patients who suffer out-of-hospital cardiac arrest have asystole as the initial recorded arrhythmia. Since they have a poor prognosis, less attention has been paid to this group of patients. AIM: To describe a consecutive population of patients with out-of-hospital cardiac arrest with asystole as the first recorded arrhythmia and to try to define indicators for an increased chance of survival in this population. SETTING: The community of Gothenburg. PATIENTS: All patients who suffered out-of-hospital cardiac arrest during 1981 to 1992 and were reached by our

emergency medical service (EMS) system and where cardiopulmonary resuscitation (CPR) was attempted. RESULTS: In all there were 3434 cardiac arrests of which 1222 (35%) showed asystole as the first recorded arrhythmia. They differed from patients with ventricular fibrillation by being younger, including more women and having a longer interval between collapse and arrival of the first ambulance. In all 90 patients (7%) were hospitalized alive and 20 (2%) could be discharged from hospital. Independent predictors for an increased chance of survival were: (a) a short interval between the collapse and arrival of the first ambulance ($P < 0.001$) and the time the collapse occurred ($P < 0.05$). Initial treatment given in some cases with adrenaline, atropine and tribonate were not associated with an increased survival. CONCLUSIONS: Of all the patients with out-of-hospital cardiac arrest, 35% were found in asystole. Of these, 7% were hospitalized alive and 2% could be discharged from hospital. Efforts should be made to improve still further the interval between collapse and arrival of the first ambulance.

1. Level of Evidence – 6
2. Methodological quality – fair (prospective observational)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – B, C
6. Relevance to the question asked - tribonat in initial treatment did not improve survival

24: Herlitz, J. et al., 1995. Survival among patients with out-of-hospital cardiac arrest found in electromechanical dissociation. *Resuscitation*, 29(2), pp.97-106.

Background: Many patients who suffer an out-of-hospital cardiac arrest are found in electromechanical dissociation at the time the Emergency Medical Service(EMS) arrives. Since they have a poor prognosis, less attention has been paid to them. Aim: To describe a consecutive population of patients with out-of-hospital cardiac arrest found in electromechanical dissociation and to try to define indicators for an increased chance of survival in this patient population, Setting: The municipality of Goteborg. Patients: All the patients who suffered an out-of-hospital cardiac arrest between 1981-1992 and were reached by our EMS system and in whom cardiopulmonary resuscitation (CPR) was attempted. Results: In all, therewere3434patientswith cardiac arrest of whom 748(22%) were found in electromechanical dissociationT.heydifferedfrompatientsfoundinventricularfibrillation as there were more women, a higher frequency of cardiac arrest during the night, a lower frequency of witnessed cardiac arrest and consequently a lower frequency of bystander-initiated CPR. In all, 96 patients (13%) were hospitalized alive and only 16 (2%) could be discharged from hospital. In a multivariate analysis relating to age, sex, time of cardiac arrest, interval between collapse and the arrival of the first ambulance, bystander- initiated CPR and treatment with adrenaline, atropine and tribonate, no independent predictor of survival was found. Conclusion: Of all the patients with out-of-hospital cardiac arrest in whom CPR was attempted by our EMS, 22% were found in electromechanical

dissociation. Of these, 13% were hospitalized alive and 2% could bed discharged from hospital. No independent predictor of an increased chance of survival was found.

1. Level of Evidence – 6
2. Methodological quality – fair (prospective observational non-target species - human)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – B, C
6. Relevance to the question asked - tribonat did not increase survival to hosp admission or discharge

25: Katz, L.M. et al., 2002. Low-dose Carbicarb improves cerebral outcome after asphyxial cardiac arrest in rats. *Annals of emergency medicine*, 39(4), pp.359-65.

Study objective: Controversy surrounds the use of buffers during cardiac arrest to correct acidosis. The objective of this study was to determine whether attenuation or neutralization of cerebral acidosis by Carbicarb alters hippocampal glutamate levels, neuronal cell death, and neurologic deficits after reper- fusion from asphyxial cardiac arrest in rats.
Methods: Rats were prospectively randomized to either a con- trol (n=45), low-dose Carbicarb (LDC; 3 mL/kg, n=45), or high- dose Carbicarb (HDC; 6 mL/kg, n=45) group in a blinded fashion during resuscitation after 8 minutes of asphyxial cardiac arrest. Microdialysis was used to assess brain pH and glutamate. A neurologic deficit score and neuronal cell death in the hippo- campus were determined at day 7.
Results: Resuscitation was greatest in LDC rats (42/45) and least in HDC rats (28/45) versus that in control rats (34/45). Brain pH was higher in the LDC and HDC rats 10 minutes after resuscitation and remained higher than that of control rats for 120 minutes after resuscitation. Glutamate levels at 10 to 120 minutes after reperfusion were lowest in the LDC rats. LDC rats had the lowest neurologic deficit score (1±2) versus that of con- trol rats (13±8) and HDC rats (19±6). Hippocampal neuronal cell death was lowest in LDC rats (30±20) versus that in control rats (86±47) and HDC rats (233±85).
Conclusion: LDC administered during resuscitation from asphyxial cardiac arrest attenuated acidosis, improved resusci- tation, and reduced neurologic deficits and the number of dead hippocampal neurons. Neutralization of cerebral acidosis with HDC increased the number of dead hippocampal neurons and neurologic deficits after resuscitation from cardiac arrest in rats.

1. Level of Evidence – 6 (non-target species - rat)
2. Methodological quality – good (RCT)
3. Magnitude of any observed effect – significant
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supports
5. Outcome(s) assessed – A

6. Relevance to the question asked - Low-dose carbicarb improved ROSC, hippocampal cell death, brain glutamate levels and neurologic deficit scores compared to high-dose or controls

26: Kette, F., Weil, M.H. & Gazmuri, R.J., 1991. Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion presssure. *JAMA : the journal of the American Medical Association*, 266(15), pp.2121-6.

Objective.: To investigate the effects of hypertonic buffer solutions on coronary perfusion pressure (CPP) and resuscitability during experimental closed-chest cardiac resuscitation.
Design.: Randomized, placebo-controlled trial. Setting.: Mammalian research laboratory.
Participants.: Forty-four domestic pigs. Interventions.: Cardiac arrest was induced by ventricular fibrillation in mechanically ventilated pigs anesthetized with pentobarbital sodium. Precordial compression was started at the third minute of untreated ventricular fibrillation and maintained for an interval of 8 minutes. A hypertonic solution of sodium bicarbonate, Carbicarb (an equimolar mixture of sodium bicarbonate and sodium carbonate [International Medication Systems, Ltd]), or sodium chloride or an isotonic solution of sodium chloride was infused into the right atrium over a 1\x=req-\ minute interval starting at the sixth minute of ventricular fibrillation. Restoration of spontaneous circulation was attempted by DC transthoracic countershock after 11 minutes of ventricular fibrillation.
Main Outcome Measures.: Plasma osmolality, CPP, and cardiac resuscitability.
Results.: Infusion of hypertonic buffer and sodium chloride solutions in- creased plasma osmolality from an average of 280 to 330 mOsm/kg. This was accompanied by a significant decrease in the aortic pressures and CPPs generated during precordial compression. No such changes occurred after infusion of isotonic sodium chloride. Restoration of spontaneous circulation, as in earlier studies, was contingent on the levels of CPP prior to attempted defibrillation. Accordingly, none of 13 animals in which the CPP declined to less than 10 mm Hg after infusion of the hypertonic solutions were successfully resuscitated. This contrasted with nine animals that received isotonic sodium chloride and served as controls. Coronary perfusion pressure consistently exceeded 10 mm Hg in these control animals, and spontaneous circulation was restored in each instance. Conclusions. : Hypertonic solutions and specifically buffer solutions administered in the absence of vasopressor agents may adversely affect cardiac resuscitation efforts by reducing CPP below critical thresholds.

1. Level of Evidence – 6 (non-target species; pig)
2. Methodological quality – good (RCT)
3. Magnitude of any observed effect – significant
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposing
5. Outcome(s) assessed – A, E=CPP

6. Relevance to the question asked - hypertonic saline, carbicarb or bicarb all decreased CPP significantly compared to normal saline; bicarb associated with decreased ROSC ($p<0.05$). CPP below critical threshold resulted in failure of ROSC

27: Kette, F. et al., 1990. Buffer agents do not reverse intramyocardial acidosis during cardiac resuscitation. *Circulation*, 81(5), pp.1660-6.

We investigated the effects of carbon dioxide-producing and carbon dioxide-consuming buffers on intramyocardial pH and on cardiac resuscitability. In 29 pigs, intramyocardial pH was continuously measured with a glass electrode advanced into the midmyocardium of the posterior left ventricle through a diaphragmatic window. Ventricular fibrillation (VF) was electrically induced by alternating current applied to the epicardium of the left ventricle. After 3 minutes of VF, precordial compression was begun and continued for an interval of 8 minutes. Sodium bicarbonate (a carbon dioxide-generating buffer), Carbicarb (a carbon dioxide-consuming buffer), and hypertonic sodium chloride (control solution) were infused into the right atrium during cardiac resuscitation. Defibrillation was attempted by transthoracic direct-current shock after 11 minutes of VF. Intramyocardial pH progressively decreased from an average value of 7.26 before VF to 6.87 before infusion of buffers. Systemic circulation and great cardiac vein pH significantly increased after administration of the two buffer agents. However, intramyocardial pH continued to decline to an average of 6.62 after 11 minutes of VF, and this decline was not altered by either buffer solution or by the saline control. As in previous studies, resuscitability was closely related to coronary perfusion pressure at the time of direct-current countershock but not to pH. Accordingly, the rationale of reversing acidosis by the administration of these buffer agents is not supported. Even more important, neither carbon dioxide-consuming nor carbon dioxide-producing buffers altered myocardial acidosis or improved myocardial resuscitability under controlled experimental conditions of cardiac arrest.

1. Level of Evidence – 6 non-target species (pig)
2. Methodological quality – good (RCT)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – A, E=intramyocardial pH
6. Relevance to the question asked - carbicarb, bicarb improved cardiac venous pH (compared to hypertonic saline) but not intramyocardial pH and did not improve ROSC

28: Kirimli, B., Harris, L.C. & Safar, P., 1969. Evaluation of sodium bicarbonate and epinephrine in cardiopulmonary resuscitation. *Anesthesia and analgesia*, 48(4), pp.649-58.

1. Level of Evidence – 3 target species (dog)

2. Methodological quality – poor - RCT, but not blinded, same dogs used again after 30 min but not crossed over into different treatment groups (i.e received bicarb +/- epi x3)
3. Magnitude of any observed effect – ? did not report statistical significance for ROSC, but animals treated with bicarbonate had lower minimum energy to successfully defibrillate, and only dogs that received bicarb + epi were successfully resuscitated all 15 times.
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – Supports
5. Outcome(s) assessed – A
6. Relevance to the question asked - 2.5mEq/kg bicarb after 2 min of CPR (after 5 min of v-fib)

29: Lathers, C.M., Tumer, N. & Schoffstall, J.M., 1989. Plasma catecholamines, pH, and blood pressure during cardiac arrest in pigs☆. *Resuscitation*, 18(1), pp.59-74.

1. Level of Evidence – 6* unable to access
2. Methodological quality – good (RCT, blinded, pig)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E=MAP, circulating catecholamines
6. Relevance to the question asked - administration of bicarb had no effect on MAP or circulating catecholamines compared to saline, however pH was significantly greater.

30: Ledingham I.M., & Norman J.N., 1962. Acid-base studies in experimental circulatory arrest. *Lancet*, 2(7263), pp.967-9.

1. Level of Evidence – 3
2. Methodological quality – poor (used controls to set up experiment, small numbers, no statistical analysis)
3. Magnitude of any observed effect – no statistical analysis, so minimal/none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supports
5. Outcome(s) assessed – E – arterial pH, PCO2, bicarbonate, SBE, post-arrest cardiac rhythm, neurologic status 24h after arrest
6. Relevance to the question asked – no bicarb (A) v. bicarb replacement 10-15 min pre-arrest based on predicted fall in BE (kg*0.43*BE, calculated from group A's values) (B) – group be had fewer arrhythmias and better neurologic recovery. Group C had variable amounts of CO2 in ventilated gas – hard to draw any conclusions

31: Leong, E.C. et al., 2001. Sodium bicarbonate improves the chance of resuscitation after 10 minutes of cardiac arrest in dogs. *Resuscitation*, 51(3), pp.309-15.

The likelihood of successful defibrillation and resuscitation decreases as the duration of cardiac arrest increases. Prolonged cardiac arrest is also associated with the development of acidosis. These experiments were designed to determine whether administration of sodium bicarbonate and/or adrenaline in combination with a brief period of cardiopulmonary resuscitation (CPR) prior to defibrillation would improve the outcome of prolonged cardiac arrest in dogs. Ventricular fibrillation (VF) was induced by a.c. shock in anaesthetised dogs. After 10 min of VF, animals received either immediate defibrillation (followed by treatment with bicarbonate or control) or immediate treatment with bicarbonate or saline (followed by defibrillation). Treatment with bicarbonate was associated with increased rates of restoration of spontaneous circulation. This was achieved with fewer shocks and in a shorter time. Coronary perfusion pressure was significantly higher in NaHCO3-treated animals than in control animals. There were smaller decreases in venous pH in NaHCO3-treated animals than in controls. The best outcome in this study was achieved when defibrillation was delayed for approximately 2 min, during which time NaHCO3 and adrenaline were administered with CPR. The results of the present study indicate that in prolonged arrests bicarbonate therapy and a period of perfusion prior to defibrillation may increase survival.

1. Level of Evidence – 3
2. Methodological quality – good (RCT)
3. Magnitude of any observed effect – significant (immediate treatment $p<0.05$, immediate defib 0.06)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supports
5. Outcome(s) assessed – A
6. Relevance to the question asked - after 10 min of v-fib, dogs treated with bicarb (2mmol/kg) + epi 0.1mg/kg had higher CPP, fewer shocks and greater ROSC than saline + epi

32: Liu, X. et al., 2002. Buffer administration during CPR promotes cerebral reperfusion after return of spontaneous circulation and mitigates post-resuscitation cerebral acidosis. *Resuscitation*, 55(1), pp.45-55.

To explore the effects of alkaline buffers on cerebral perfusion and cerebral acidosis during and after cardiopulmonary resuscitation (CPR), 45 anaesthetized piglets were studied. The animals were subjected to 5 min non-interventional circulatory arrest followed by 7 min closed chest CPR and received either 1 mmol/kg of sodium bicarbonate, 1 mmol/kg of tris buffer mixture, or the same volume of saline (n=15 in all groups), adrenaline (epinephrine) boluses and finally external defibrillatory shocks. Systemic haemodynamic variables, cerebral cortical blood flow, arterial, mixed venous, and internal jugular bulb blood acid-base status and blood gases as well as cerebral tissue pH and PCO(2) were monitored. Cerebral tissue acidosis was recorded much earlier than

arterial acidaemia. After restoration of spontaneous circulation, during and after temporary arterial hypotension, pH in internal jugular bulb blood and in cerebral tissue as well as cerebral cortical blood flow was lower after saline than in animals receiving alkaline buffer. Buffer administration during CPR promoted cerebral cortical reperfusion and mitigated subsequent post-resuscitation cerebral acidosis during lower blood pressure and flow in the reperfusion phase. The arterial alkalosis often noticed during CPR after the administration of alkaline buffers was caused by low systemic blood flow, which also results in poor outcome.

1. Level of Evidence – 6
2. Methodological quality – good (RCT non-target species - piglet)
3. Magnitude of any observed effect – ROSC - (P>0.006); cerebral perfusion pressure (P<0.001)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – Supporting
5. Outcome(s) assessed – A, E=cerebral blood flow
6. Relevance to the question asked - 5min VF before CPR, then randomized to 1mmol/kg tribonat v. 1mmol/kg bicarb v. saline. Greater ROSC in buffer groups, also looked at CPP, cerebral oxygen extraction, cerebral pH. Tris group had greater ROSC than bicarb (p=0.046) but confounded by lower CPP in bicarb group before intervention.

33: Makino, J. et al., 2005. A quantitative analysis of the acidosis of cardiac arrest: a prospective observational study. *Critical care (London, England)*, 9(4), pp.R357-62.

INTRODUCTION: Metabolic acidosis is common in patients with cardiac arrest and is conventionally considered to be essentially due to hyperlactatemia. However, hyperlactatemia alone fails to explain the cause of metabolic acidosis. Recently, the Stewart-Figge methodology has been found to be useful in explaining and quantifying acid-base changes in various clinical situations. This novel quantitative methodology might also provide useful insight into the factors responsible for the acidosis of cardiac arrest. We proposed that hyperlactatemia is not the sole cause of cardiac arrest acidosis and that other factors participate significantly in its development. METHODS: One hundred and five patients with out-of-hospital cardiac arrest and 28 patients with minor injuries (comparison group) who were admitted to the Emergency Department of a tertiary hospital in Tokyo were prospectively included in this study. Serum sodium, potassium, ionized calcium, magnesium, chloride, lactate, albumin, phosphate and blood gases were measured as soon as feasible upon arrival to the emergency department and were later analyzed using the Stewart-Figge methodology. RESULTS: Patients with cardiac arrest had a severe metabolic acidosis (standard base excess -19.1 versus -1.5; P < 0.0001) compared with the control patients. They were also hyperkalemic, hypochloremic, hyperlactatemic and hyperphosphatemic. Anion gap and strong ion gap were also higher in cardiac arrest patients. With the comparison group as a reference, lactate was found to be the strongest determinant of acidosis (-11.8 meq/l), followed by strong ion gap (-7.3 meq/l) and phosphate (-2.9 meq/l). This metabolic acidosis was attenuated by the alkalinizing effect of hypochloremia (+4.6 meq/l), hyperkalemia (+3.6

meq/l) and hypoalbuminemia (+3.5 meq/l). CONCLUSION: The cause of metabolic acidosis in patients with out-of-hospital cardiac arrest is complex and is not due to hyperlactatemia alone. Furthermore, compensating changes occur spontaneously, attenuating its severity.

1. Level of Evidence – 6
2. Methodological quality – fair (prospective observation)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E=acid/base status
6. Relevance to the question asked - quantitative acid/base analysis CPA v. ABGs of patients with minor injuries

lactate was found to be the strongest determinant of acidosis (-11.8 meq/l), followed by strong ion gap (-7.3 meq/ l) and phosphate (-2.9 meq/l). This metabolic acidosis was attenuated by the alkalinizing effect of hypochloremia (+4.6 meq/l), hyperkalemia (+3.6 meq/l) and hypoalbuminemia (+3.5 meq/l) - complex

34: Martinez, L.R. et al., 1979. pH homeostasis during cardiopulmonary resuscitation in critically ill patients. *Resuscitation*, 7(2), pp.109-17.

We investigated the effect of repeated administration of sodium bicarbonate on acid-base balance and serum chemistry in a group of patients who developed cardiac arrest. A mixed acidosis persisted throughout the duration of resuscitation in the majority of patients in spite of the large ventilatory volume and multiple doses of bicarbonate they received. However, the repeated administration of bicarbonate prevented a severe fall in serum pH. Our study demonstrated the beneficial role of bicarbonate in the treatment of metabolic acidosis associated with cardiac arrest of prolonged duration. Analysis of our data strongly indicated that the primary factors which determine the serum pH during cardiopulmonary resuscitation are the duration of circulatory arrest, adequacy of ventilation and circulation, pH immediately before arrest, and quantity of bicarbonate administered and its volume of distribution in the various fluid and tissue compartments.

1. Level of Evidence – 6* could not access
2. Methodological quality – poor (prospective observation, no controls)
3. Magnitude of any observed effect – unknown (abstract only)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E=pH
6. Relevance to the question asked - mixed acidosis persisted despite bicarb + high ventilatory rate but bicarb improved pH

Minuck, M. & Sharma, G.P., 1977. Comparison of THAM and sodium bicarbonate in resuscitation of the heart after ventricular fibrillation in dogs. *Anesthesia and analgesia*, 56(1), pp.38-45.

Tris (hydroxymethyl) aminomethane (tromethamine or THAM) has been suggested as an effective substitute for sodium bicarbonate (NaHCO3) in the treatment of metabolic acidosis accompanying cardiac arrest. Even though several reports on its appraisal have been published, there is still no clear agreement on its therapeutic value. A double-blind study was therefore undertaken to compare in 36 dogs the effectiveness of 0.6 M THAM, 0.3 M THAM, and NaHCO3 (0.892 mEq/ml) to correct metabolic acidosis produced during 3 minutes of cardiac fibrillation, followed by a 3-minute period of cardiac compression. The dogs were then defibrillated and observed for 45 minutes. One group of 8 dogs was treated with 0.9 percent NaCl infusion. Compared with 0.9 percent NaCl, both THAM and NaHCO3 were equally effective in correcting metabolic acidosis (p less than 0.05). Initially, 0.6 M THAM produced a more pronounced (p less than 0.05) elevation of blood pH, but this effect was not sustained during the later postdefibrillation period. There was little difference in the effect of either of these drugs on mean aortic pressure and total peripheral vascular resistance. It is concluded that adequate ventilation and effective cardiac compression are still the chief criteria on which the final outcome of cardiac resuscitation depends. Correction of metabolic acidosis is important supportive therapy, but either THAM or NaHCO3 can be used with comparatively equivalent effect.

1. Level of Evidence – 3 target species (dog)
2. Methodological quality – neutral (RCT blinded but no control)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – A
6. Relevance to the question asked - 36 dogs - bicarb, 2 conc of THAM v. saline after fibrillation x3 min followed by cpr x3 min followed by defibrillation. bicarb and THAM had equal effects on correcting pH, no effect on MAP or resuscitatability

36: Neumar, R.W. et al., 1995. Epinephrine and sodium bicarbonate during CPR following asphyxial cardiac arrest in rats. *Resuscitation*, 29(3), pp.249-63.

Although high-dose epinephrine during CPR improves coronary perfusion pressure (CoPP) and rate of return of spontaneous circulation (ROSC) in some models, its impact on long term outcome (> or = 72 h) has not been evaluated. Previous studies of sodium bicarbonate (NaHCO3) therapy during CPR indicate that beneficial effects may be dependent on epinephrine (EPI) dose. We hypothesized that EPI and NaHCO3 given during CPR have a significant impact on long term outcome. One hundred male Sprague-Dawley rats were prospectively studied in a block randomized placebo controlled trial. Rats were anesthetized, paralyzed, mechanically ventilated, instrumented, and each underwent 10 min of asphyxia, resulting in 6.8 +/- 0.4 min of circulatory arrest. Resuscitation was performed by mechanical ventilation and manual external chest compressions. EPI 0.0 (placebo), 0.01, 0.1, or 1.0 mg/kg IV was given at the onset of CPR, followed by NaHCO3 0.0 (placebo) or 1.0 mEq/kg IV. Successfully resuscitated rats were monitored and ventilated for 1 h without hemodynamic support. Neurologic deficit scores (NDS), cerebral histopathologic damage scores (CHDS) and myocardial

histopathologic damage scores (MHDS) were determined in rats that survived 72 h. EPI improved CoPP and ROSC in a dose-dependent manner up to 0.1 mg/kg. Rats receiving EPI 0.1 and 1.0 mg/kg during CPR exhibited prolonged post-ROSC hypertension and metabolic acidemia, increased A-a O2 gradient, and an increased incidence of post-ROSC ventricular tachycardia or fibrillation. Overall survival was lower with EPI 0.1 and 1.0 mg/kg compared to 0.01 mg/kg. Although NDS was significantly less with EPI 0.1 mg/kg compared to placebo, there was no difference in CHDS between groups. In contrast, MDS was significantly higher with EPI 0.1 mg/kg compared to placebo or EPI 0.01 mg/kg. There was an overall trend toward improved survival at 72 h in rats that received NaHCO3 which was most evident in the EPI 0.1 mg/kg group. We conclude that (1) EPI during CPR has a biphasic dose/response curve in terms of survival, when post-resuscitation effects are left untreated and (2) NaHCO3 doses greater than 1.0 mEq/kg may be necessary to treat the side-effects of high-dose EPI. Further work is needed to determine if treating the immediate post-resuscitation effects of high-dose EPI can prevent detrimental effects on long-term outcome.

1. Level of Evidence – 6
2. Methodological quality – good (double blind RCT, rats)
3. Magnitude of any observed effect – non-significant (p=0.17)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral (non-significant)
5. Outcome(s) assessed – A; (also E=Neurologic deficit scores (NDS), cerebral histopathologic damage scores (CHDS) and myocardial histopathologic damage scores (MHDS) @72h)
6. Relevance to the question asked - non-significant trend towards increase rosc in rats receiving high dose epi (0.1mg/kg) with 1 meq/kg bicarb v. placebo + high-dose epi. asphyxia model

37: von Planta, M. et al., 1989. Myocardial acidosis associated with CO2 production during cardiac arrest and resuscitation. *Circulation*, 80(3), pp.684-92.

Previous studies from our institution demonstrated significant hypercarbic acidosis in the mixed venous (pulmonary artery) blood in animals and human patients during cardiac arrest and cardiopulmonary resuscitation (CPR). In the present study, the acid-base state of the myocardium during cardiac arrest was investigated. Cardiac arrest was electrically induced in 11 pentobarbital-anesthetized and mechanically ventilated domestic pigs. Precordial compression was begun 3 minutes after onset of ventricular fibrillation and continued for 8 minutes. During CPR, there was rapid onset of profound myocardial acidosis with an increase in intramyocardial [H+] from 54 +/- 5 to 146 +/- 20 nmol/l (7.27 +/- 0.04 to 6.88 +/- 0.20 pH units). Great cardiac vein PCO2 increased from 57 +/- 2 to 158 +/- 12 mm Hg. Profound hypercarbic acidosis in great cardiac vein blood was associated with myocardial lactate production to levels of 8.1 +/- 0.7 mmol/l. Only moderate decreases in cardiac vein bicarbonate concentrations from 31 +/- 1 to 23 +/- 1 mmol/l were observed. These acid-base changes were almost completely reversed over an interval of 60 minutes after the animals were successfully resuscitated by DC

countershock. The PCO2 in cardiac vein blood was significantly greater than that of mixed venous blood, demonstrating disproportionate myocardial production of CO2 during CPR. Accordingly, it is CO2 production during ischemia that is implicated as the predominant mechanism accounting for myocardial [H+] increases during cardiac arrest. Important clinical implications for buffer therapy during CPR and, in particular, treatment with bicarbonate emerge from these observations.

1. Level of Evidence – 6
2. Methodological quality – fair (experimental observational pigs)
3. Magnitude of any observed effect – NA
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E=myocardial pH, CO2 production
6. Relevance to the question asked - myocardial acidosis is due to lactate and CO2 production "only minor effects on tissue bicarb"

38: Redding, J.S. & Pearson, J.W., 1968. Resuscitation From Ventricular Fibrillation: Drug Therapy. *JAMA*, 203(4), pp.255-260.

In resuscitating dogs subjected to ten minutes of circulatory arrest due to ventricular fibrillation, a number of drugs were used with artificial ventilation of the lungs, external cardiac massage, and external electrical counter-shock. Resuscitation was more successful when epinephrine was used than when no drug therapy or sodium bicarbonate were used. Combination of lidocaine with epinephrine increased the frequency of defibrillation, but circulation was not restored more often than with epinephrine alone. The use of methoxamine hydrochloride was followed by successful resuscitation more often than was the use of epinephrine. Combination of epinephrine and sodium bicarbonate was as effective as methoxamine in restoring circulation, and inspection of the survivors after 24 hours suggested that the combination might be preferable.

1. Level of Evidence – 3
2. Methodological quality – fair - RCT not blinded, doses not scaled
3. Magnitude of any observed effect – bicarb alone - none, bicarb + epi improved ROSC and survival past 24h
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supportive
5. Outcome(s) assessed – A
6. Relevance to the question asked - bicarb + epi improved survival compared to epi alone (all dogs got 1mg epi = ~0.1mg/kg)

39: Reynolds, J.C., Rittenberger, J.C. & Menegazzi, J.J., 2007. Drug administration in animal studies of cardiac arrest does not reflect human clinical experience. *Resuscitation*, 74(1), pp.13-26.

INTRODUCTION: To date, there is no evidence showing a benefit from any advanced cardiac life support (ACLS) medication in out-of-hospital cardiac arrest (OOHCA),

despite animal data to the contrary. One explanation may be a difference in the time to first drug administration. Our previous work has shown the mean time to first drug administration in clinical trials is 19.4min. We hypothesized that the average time to drug administration in large animal experiments occurs earlier than in OOHCA clinical trials. METHODS: We conducted a literature review between 1990 and 2006 in MEDLINE using the following MeSH headings: swine, dogs, resuscitation, heart arrest, EMS, EMT, ambulance, ventricular fibrillation, drug therapy, epinephrine, vasopressin, amiodarone, lidocaine, magnesium, and sodium bicarbonate. We reviewed the abstracts of 331 studies and 197 full manuscripts. Exclusion criteria included: non-peer reviewed, all without primary animal data, and traumatic models. From these, we identified 119 papers that contained unique information on time to medication administration. The data are reported as mean, ranges, and 95% confidence intervals. Mean time to first drug administration in animal laboratory studies and clinical trials was compared with a t-test. Regression analysis was performed to determine if time to drug predicted ROSC. RESULTS: Mean time to first drug administration in 2378 animals was 9.5min (range 3.0-28.0; 95% CI around mean 2.78, 16.22). This is less than the time reported in clinical trials (19.4min, $p<0.001$). Time to drug predicted ROSC (odds ratio 0.844; 95% CI 0.738, 0.966). CONCLUSION: Shorter drug delivery time in animal models of cardiac arrest may be one reason for the failure of animal studies to translate successfully into the clinical arena.

1. Level of Evidence – 6
2. Methodological quality – good (metanalysis)
3. Magnitude of any observed effect – large
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E=time to first drug administration
6. Relevance to the question asked - brings up a good point about comparing experimental trials to clinical - drugs are given to animals in studies at avg 9.5 min; human clinical trials at 19.4min

40: Roberts, D. et al., 1990. Early predictors of mortality for hospitalized patients suffering cardiopulmonary arrest. *Chest*, 97(2), pp.413-9.

Few if any prearrest or intraarrest variables have been identified as highly predictive of inhospital mortality following cardiopulmonary arrest. A total of 310 consecutive patients requiring advanced cardiac life support during the calendar years 1985 and 1986 were reviewed with respect to eight specific variables. These included age, diagnosis, location, mechanism of the event, duration of resuscitation, whether the event was witnessed or unwitnessed, the initial observed rhythm and medications administered. A total of 37.1 percent of the patients were successfully resuscitated, but only 9.7 percent survived until discharge. Factors strongly associated with inhospital mortality included unwitnessed events ($p = 0.0316$), the need for epinephrine ($p = 0.0003$), identification of electromechanical dissociation or asystole as initial rhythms ($p = 0.0000$), and cardiac vs respiratory mechanism of arrest ($p = 0.0000$).

1. Level of Evidence – 6

2. Methodological quality – poor (retrospective, human)
3. Magnitude of any observed effect – $p<0.0005$
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposes
5. Outcome(s) assessed – C
6. Relevance to the question asked - administration of bicarb or epi were strongly associated with increased in-hospital mortality

41: Rosenberg, J.M. et al., 1989. The effect of CO2 and non-CO2-generating buffers on cerebral acidosis after cardiac arrest: A 31P NMR study. *Annals of emergency medicine*, 18(4), pp.341-7.

There is controversy regarding the use of alkalinizing agents during reperfusion after cardiac arrest. The potential deleterious effects of sodium bicarbonate (bicarb) administration, including paradoxic cerebral acidosis, have led to the search for alternative agents. Tromethamine (tris) is a non-CO2-generating buffer that has been proposed for use during cardiopulmonary resuscitation. The purpose of this experiment was to compare the ability of tris with bicarb to correct brain pH (pH B) during reperfusion after a 12-minute cardiac arrest. Adult mongrel dogs were instrumented and placed in the bore of a Bruker Biospec 1.89 tesla superconducting magnet system. Ventricular fibrillation was induced; after 12 minutes, cardiopulmonary bypass was initiated and maintained for two hours with minimum flows of 80 mL/kg/min. Bicarb (n = 5) or tris (n = 5) were administered to correct arterial pH as rapidly as possible. 31P NMR spectra were obtained at baseline and throughout ischemia and reperfusion. The pH B was determined with the inorganic phosphate relative to the phosphocreatine resonance signal shift. Profile analysis indicates a difference between groups (P less than .02) related to an initial delay in pH B correction in the tris group. By 48 minutes of reperfusion, pH B did not differ between the groups. Moreover, there was no evidence of paradoxic cerebral acidosis in the bicarb group. Although tris corrects blood pH as quickly as bicarb, it is less effective in correcting pH B. Absence of paradoxic acidosis may be caused by efficient elimination of CO2 by cardiopulmonary bypass.
1. Level of Evidence – 3* cannot access
2. Methodological quality – poor - animals were on bypass
3. Magnitude of any observed effect – neutral
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E=cerebral pH
6. Relevance to the question asked - tris v. bicarb; tris less effective, no paradoxic cerebral acidosis but animals were on bypass

42: Rubertsson, S. & Wiklund, L., 1993. Hemodynamic effects of epinephrine in combination with different alkaline buffers during experimental, open-chest, cardiopulmonary resuscitation. *Critical care medicine*, 21(7), pp.1051-7.

Abstract OBJECTIVE: To evaluate the hemodynamic actions of epinephrine combined with different alkaline buffers during experimental, open-chest, cardiopulmonary resuscitation (CPR).
DESIGN: Prospective, randomized, controlled trial.
SETTING: Experimental animal laboratory in a university hospital.
SUBJECTS: A total of 28 anesthetized piglets.
INTERVENTIONS: After catheterization and application of a pulmonary artery flow probe (transit-time ultrasound flowmetry), the animals were stabilized. Induction of ventricular fibrillation was followed by a 15-min period of CPR, including manual heart compressions and mechanical ventilation with pure oxygen. On commencement of CPR, a 4-min alkaline buffer infusion began, with 50 mmol of sodium bicarbonate (n = 7), tris buffer mixture (n = 7), or tris buffer (n = 7), or, as a control (n = 7), the same volume of normal saline. After 8 mins of CPR, 0.5 mg of epinephrine was given intravenously; after 15 mins, direct current shocks were used to revert the heart to sinus rhythm.
MEASUREMENTS AND MAIN RESULTS: Blood flow measured in the pulmonary artery during open-chest CPR was approximately 20% of normal cardiac output. Administration of epinephrine reduced pulmonary artery flow irrespective of buffer. Sodium bicarbonate alone resulted in higher systemic blood pressure than pure tris: tris buffer mixture and normal saline were intermediate. Sodium bicarbonate combined with epinephrine tended to produce lower systemic blood pressure than other combinations.
CONCLUSIONS: Experimental open-chest CPR generates pulmonary artery blood flows (20% of normal cardiac output) that are at best at the lower level of those blood flow rates previously reported (25% to 40% of normal cardiac output) from studies of closed-chest CPR. Different alkaline buffers influence circulatory and acid-base parameters differently before and after administration of epinephrine.

1. Level of Evidence – 6
2. Methodological quality – good (RCT, pigs)
3. Magnitude of any observed effect – none (resuscitatability)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E= PAP, MAP
6. Relevance to the question asked - 15 min of CPR after vfib; tris buffer v. tris mix v. bicarb v. saline, followed by epi (0.5mg total, not scaled); no effect on PAP, initially MAP higher in bicarb group but increase in MAP after epi was smaller in bicarb group

43: Sanders, A.B. et al., 1990. The role of bicarbonate and fluid loading in improving resuscitation from prolonged cardiac arrest with rapid manual chest compression CPR. *Annals of emergency medicine*, 19(1), pp.1-7.

Rapid manual chest compression (120 compressions/min) CPR has been shown to improve hemodynamics and survival when compared with standard CPR (60 compressions/min) in a canine model of prolonged cardiac arrest. The study showing improved survival with rapid manual CPR empirically included treatment with bicarbonate and initial fluid loading. To determine the role of bicarbonate and fluid loading in the success of rapid manual chest compression CPR, 31 mongrel dogs were

studied. After instrumentation with micromanometer-tipped catheters to measure aortic and right atrial pressures, the animals were assigned sequentially to three treatment groups. Group A underwent rapid manual chest compressions at 120 compressions/min, bicarbonate treatment, and initial fluid loading. Group B underwent rapid manual compressions at 120 compressions/min without bicarbonate or fluid loading. Group C underwent standard CPR at 80 compressions/min with bicarbonate and fluid loading. After 30 minutes of ventricular fibrillation, defibrillation was attempted. Seven of 11 dogs in group A survived 24 hours. None of the animals in group B resuscitated or survived. Three of the ten dogs in group C survived 24 hours. Survival with rapid manual CPR without bicarbonate and initial fluid loading was significantly less than when these interventions were used ($P < .01$). To examine the separate contribution of bicarbonate and fluid therapy, two additional groups of animals were studied. Fourteen animals (group D) received rapid manual CPR with bicarbonate therapy, and 12 (group E) received rapid manual CPR with fluid loading only. Three of 14 in group D and two of 12 in group E survived 24 hours. This study confirms the benefit of using rapid manual chest compression CPR compared with standard CPR. However, use of bicarbonate and fluid loading is necessary to achieve improved outcome with rapid manual chest compression CPR.

1. Level of Evidence – 3* cannot access
2. Methodological quality – good (RCT, dog)
3. Magnitude of any observed effect – significant
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supports
5. Outcome(s) assessed – A
6. Relevance to the question asked - rapid manual compressions (120bpm) with bicarb and fluid loading improved ROSC

44: Sanders, A.B. et al., 1988. Acid-base balance in a canine model of cardiac arrest. *Annals of emergency medicine*, 17(7), pp.667-71.

Our study was performed to determine the pattern of arterial, venous, and cerebral spinal fluid (CSF) acidosis in a canine model of cardiac arrest and resuscitation; and the effect of bicarbonate treatment on arterial, venous, and CSF acidosis. Animals were instrumented to sample arterial blood, mixed venous blood, and CSF through a cisternal catheter. Following six minutes of ventricular fibrillation, manual CPR efforts were begun and continued for 30 minutes of cardiac arrest. Arterial, mixed venous, and CS fluids were sampled at baseline, six, 12, 18, 24, 27, and 30 minutes. Ten experimental dogs received sodium bicarbonate (2 mEq/kg) at 20 minutes of cardiac arrest, while ten animals in the control group received no alkali treatment. The experimental group showed a significantly higher arterial (7.79 +/- 0.20 vs 7.46 +/- 0.16 at 30 minutes) and venous pH (7.34 +/- 0.12 vs 7.19 +/- 0.10 at 24 minutes) following bicarbonate administration. This higher pH occurred despite a concomitant increase in arterial (31 +/- 10 vs 19 +/- 9 mm Hg at 27 minutes; 31 +/- 9 vs 10 +/- 8 at 30 minutes) and venous (104 +/- 30 vs 63 +/- 10 mm Hg at 24 minutes) pCO_2. CSF analysis showed a gradually

worsening acidosis. However, CSF pH (7.12 +/- 0.14 vs 7.16 +/- 0.23 at 30 minutes) and pCO2 were not significantly changed by the administration of bicarbonate.

1. Level of Evidence – 3* cannot access
2. Methodological quality – good (RCT)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – E=CSF pH, pCO2
6. Relevance to the question asked - no change in cerebral acidosis with bicarbonate administration

45: Skovron, M.L., Goldberg, E. & Suljaga-Petchel, K., 1985. Factors predicting survival for six months after cardiopulmonary resuscitation: multivariate analysis of a prospective study. *The Mount Sinai journal of medicine, New York*, 52(4), pp.271-5.

1. Level of Evidence – ****unable to access even an abstract
2. Methodological quality –
3. Magnitude of any observed effect –
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed –
5. Outcome(s) assessed –
6. Relevance to the question asked –

46: Stiell, I.G. et al., 1995. Association of drug therapy with survival in cardiac arrest: limited role of advanced cardiac life support drugs. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*, 2(4), pp.264-73.

Objective: To generate hypotheses regarding the association of standard Advanced Cardiac Life Support (ACLS) drugs with human cardiac arrest survival. Methods: This observational cohort study was conducted over a two-year period in the wards, intensive care units, and EDs of two tertiary care hospitals. Included were adult patients who suffered cardiac arrest either inside or outside the hospital and who required epinephrine according to standard ACLS guidelines. Six standard ACLS drugs (given while CPR was in progress) were assessed for association with survival from resuscitation to one hour and to hospital discharge by univariate and multivariate logistic regression analyses. Results: In the 529 patients studied, initial cardiac rhythm had no impact on the association between drug administration and survival. The time of drug administration (quartile of ACLS period) was associated with resuscitation for atropine ($p < 0.05$) and lidocaine ($p < 0.01$). The odds ratios (95% CIs) for successful resuscitation, after multivariate adjustment for potential confounders, were: a respiratory initiating cause, 3.7 (2.1–6.4); each 5-minute increase in CPR-ACLS interval, 0.5 (0.4–0.7); each 5-minute duration of ACLS, 0.9 (0.8–1.0); atropine, 1.2 (1.0–1.3); bretylium, 0.4 (0.1–1.1); calcium, 0.8 (0.2–2.4); lidocaine, 0.9 (0.7–1.1); procainamide, 21.0 (5.2–84.0); and sodium bicarbonate 1.2 (1.0–1.6). All other potential confounding variables entered into

the model were not significantly associated with resuscitation. Conclusion: Initiating cause of arrest, time to ACLS, and duration of ACLS were important correlates of survival. Other than procainamide, standard ACLS drugs had relatively little association with survival, but timing of administration may be an important factor. Further research using definitive large randomized controlled trials is warranted to assess the role of drug therapy in improving cardiac arrest survival.

1. Level of Evidence – 6
2. Methodological quality – fair (observational cohort)
3. Magnitude of any observed effect – small (OR 1.2)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supporting
5. Outcome(s) assessed – A
6. Relevance to the question asked - bicarb administration had a slight increase in odds ratio for ROSC, much less than cause of arrest, time to ACLS, duration

47: Suljaga-Pechtel, K. et al., 1984. Cardiopulmonary resuscitation in a hospitalized population: prospective study of factors associated with outcome. *Resuscitation*, 12(2), pp.77-95.

A prospective study of advanced cardiopulmonary resuscitation (CPR) was carried out on 226 patients in order to examine factors predicting successful resuscitation and 6 month survival. The mean age of all patients was 70 years and median age was 74. Cardiopulmonary resuscitation was successful in 40.5% (137) of all arrests and in 48.7% (110) of the first arrests. Thirty of 207 patients with one or more cardiac arrests were discharged alive (14%). Twenty-one of our patients were alive at 6 months (10.3%). Patients in ventricular fibrillation and/or ventricular tachycardia at the time of arrest were more likely to have successful outcomes. When the patient required Isuprel or bicarbonate, cardiopulmonary resuscitation was significantly less successful. We found no correlation of immediate outcome with the following variables: location of arrest; time of day; pre-existence of shock; coma; stroke; malignancy. Uremia and/or chronic obstructive pulmonary disease was not significantly associated with failed resuscitation. Most notable in our results of specific treatments was the evidence for the need to improve the initial pH, particularly when it was less than 7.2. Failure to do so by the time the second blood gas was drawn was associated with failure of cardiopulmonary resuscitation. Our results also suggest that the adequate treatment of metabolic acidosis, and improved ventilatory management with improved PO2 and optimization of PCO2, play a role in the better outcome of cardiopulmonary resuscitation.

1. Level of Evidence – 6 * unable to access
2. Methodological quality – fair - prospective observational cohort
3. Magnitude of any observed effect – significant
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposing
5. Outcome(s) assessed – A
6. Relevance to the question asked - use of isuprel or bicarb significantly decreased ROSC

48: Sun, S. et al., 1996. Effects of buffer agents on postresuscitation myocardial dysfunction. *Critical care medicine*, 24(12), pp.2035-41

Earlier studies demonstrated that hypertonic buffer agents administered during cardiopulmonary resuscitation (CPR) altered neither myocardial pH nor cardiac resuscitability. The rationale for the routine use of buffer agents for CPR has therefore been challenged. However, when these buffer agents are administered during CPR, they may have favorable effects on the postresuscitation course. Postresuscitation myocardial dysfunction has more recently emerged as a potentially fatal complication after successful cardiac resuscitation. Options for prevention and management of this complication have prompted the present studies, in which the effects of buffer agents administered during CPR are evaluated as to their effects on postresuscitation myocardial function and survival. Objectives: Earlier studies demonstrated that hypertonic buffer agents administered during cardiopulmonary resuscitation (CPR) altered neither myocardial pH nor cardiac resuscitability. The rationale for the routine use of buffer agents for CPR has therefore been challenged. However, when these buffer agents are administered during CPR, they may have favorable effects on the postresuscitation course. Postresuscitation myocardial dysfunction has more recently emerged as a potentially fatal complication after successful cardiac resuscitation. Options for prevention and management of this complication have prompted the present studies, in which the effects of buffer agents administered during CPR are evaluated as to their effects on postresuscitation myocardial function and survival. Design: Prospective, randomized, controlled animal study. Setting: University animal laboratory. Subjects: Forty male Sprague-Dawley rats (450 to 570 g). Interventions: Ventricular fibrillation was induced electrically. Mechanical ventilation and precordial compression were initiated after either a 4- or an 8-min interval of untreated cardiac arrest. Sodium bicarbonate as a CO2-generating buffer, Carbicarb [R] and tromethamine as CO2-consuming buffers, or hypertonic saline placebo were injected as a bolus into the right atrium during CPR. Defibrillation after 10 mins of cardiac arrest and CPR was successful in each instance. No differences in the electric power required for successful resuscitation were documented. Left ventricular pressure, rate of left ventricular pressure increase measured at a left ventricular pressure of 40 mm Hg (dP/dt40), rate of left ventricular pressure decline (-dP/dt), and end-tidal PCO2 were continuously measured for 240 mins after successful resuscitation. Measurements and Main Results: Decreases in coronary perfusion pressure were observed after each buffer or placebo injection. As anticipated, end-tidal PCO2 increased after bicarbonate and decreased after Carbicarb or tromethamine. Postresuscitation left ventricular function was significantly decreased in all animals. However, there was significantly less depression in rate of left ventricular pressure increase measured at a left ventricular pressure of 40 mm Hg (dP/dt40), rate of left ventricular pressure decline (-dP/dt), and a lower left ventricular diastolic pressure with both Carbicarb and tromethamine in association with significant increases in postresuscitation survival rate. When the duration of untreated cardiac arrest was increased to 8 mins, the severity of postresuscitation left ventricular dysfunction was magnified and postresuscitation myocardial function and survival were significantly

improved with both CO2-generating and CO2-consuming buffer agents. Conclusion: Although buffer agents may not improve the success of resuscitation when administered during CPR, they may ameliorate postresuscitation myocardial dysfunction and thereby improve postresuscitation survival.

1. Level of Evidence – 6
2. Methodological quality – good (rats, RCT)
3. Magnitude of any observed effect – significant
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – support
5. Outcome(s) assessed – E=LV function
6. Relevance to the question asked - 10 min vfib rats; those that received carbicarb or tromethamine had less decrement in LV function; with increased length of untreated arrest (8min) arrest, all buffers improved LV function

49: Sun, S. et al., 1999. Combined effects of buffer and adrenergic agents on postresuscitation myocardial function. *The Journal of pharmacology and experimental therapeutics*, 291(2), pp.773-7.

Although buffer agents alone have failed to improve the success of resuscitation, we now examine the widely held concept that it is the combined effect of alkaline buffer and adrenergic agents that improves outcomes of cardiopulmonary resuscitation. In the present report, the effects of both CO(2)-consuming and CO(2)-generating buffer agents in combination with adrenergic vasopressor drugs were investigated. Ventricular fibrillation was electrically induced in Sprague-Dawley rats weighing between 450 and 550 g. Precordial compression and mechanical ventilation were initiated after 8 min of untreated ventricular fibrillation. Animals were then randomized to receive bolus injections of either inorganic sodium bicarbonate buffer, organic tromethamine buffer, or saline placebo. The beta(1) adrenergic effects of epinephrine were blocked with esmolol. The vasopressor amine was injected 2 min after injection of the buffer agent. Electrical defibrillation was attempted at the end of 8 min of precordial compression. In 15 additional animals, the sequence of administration of the adrenergic vasopressor and buffer agents was reversed such that the adrenergic vasopressor was injected before the buffer agents. All animals were restored to spontaneous circulation. Both bicarbonate and tromethamine significantly decreased coronary perfusion pressure from 26 to 15 mm Hg and reduced the magnitude of the vasopressor effect of the adrenergic vasopressor. When the vasopressor preceded the buffer, declines in coronary perfusion pressure after administration of buffer agents were prevented. In each instance, however, greater impairment of postresuscitation myocardial function and decreased postresuscitation survival were observed after treatment with buffer agents.

1. Level of Evidence – 6
2. Methodological quality – good (RCT, rats)
3. Magnitude of any observed effect – significant
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposing
5. Outcome(s) assessed – E=CPP, LV function

6. Relevance to the question asked - 8 min vfib induced in rats, epi+bicarb or tromethamine v. placebo - decreased CPP with either buffer, less depression LV function if buffer preceded epi

50: Telivuo, L. et al., 1968. Comparison of alkalizing agents in resuscitation of the heart after ventricular fibrillation. *Annales chirurgiae et gynaecologiae Fenniae*, 57(2), pp.221-4.

1. Level of Evidence – *unable to access even an abstract
2. Methodological quality –
3. Magnitude of any observed effect –
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed –
5. Outcome(s) assessed –
6. Relevance to the question asked –

51: Vanags, B. et al., 1989. Interventions in the therapy of electromechanical dissociation. *Resuscitation*, 17(2), pp.163-71.

Abstract Electromechanical dissociation (EMD) is a major arrest rhythm for which there is often inadequate treatment. The purpose of this study was to evaluate the different pharmacological and non-pharmacological interventions considered in the treatment of EMD. During the 6-year period, January 1st, 1980 to December 31st, 1985, 503 evaluable adult patients presented in a non-traumatic, non-poisoning cardiopulmonary arrest with the initial rhythm of EMD. One hundred nineteen patients obtained a pulse during resuscitation efforts following drug administration. The average time to obtaining pulses after the last drug administration was 1.97 ± 2.21 min. The following drugs were last administered prior to transient pulses: bicarbonate, (26%); epinephrine, (22%); atropine, (22%); dopamine, (11%); calcium, (9%); isoproterenol, (6%); other drugs, (4%). Ninety-five percent of the successful resuscitations received eight or less drug interventions and all saves received three or less drug interventions. Two hundred twenty-four patients (44.5%) had 288 non-pharmacological interventions. Twenty-three patients developed a pulse after intervention in the following distribution: MAST suit (N = 9), pericardiocentesis (N = 6), fluid challenge (N = 5), needle thoracostomy (N = 1), and intervention combinations (N = 2). The time interval between intervention and the onset of pulse was as follows: MAST suit, 4 ± 2.8 min; pericardiocentesis, 3.7 ± 3.6 min; fluid challenge, 4.8 ± 4.1 min; needle thoracostomy, 6 min. The overall save rate for intervention patients was 0.9% whereas for those not having intervention it was 7.2% (P 0.0003). In conclusion, the apparent association of atropine with the attainment of a pulse suggests that this drug ought to be considered as a therapy for EMD and that the use of non-pharmacological interventions are not associated with any improvement in survival.
Keywords: Electromechanical dissociation; Bicarbonate; Epinephrine; Atropine; Isoproterenol; Prehospital cardiac arrest; Pericardiocentesis; Fluid challenge; MAST suit; Needle thoracostomy

1. Level of Evidence – 6*unable to access, not enough info in abstract
2. Methodological quality –
3. Magnitude of any observed effect –
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed –
5. Outcome(s) assessed –
6. Relevance to the question asked –

52: Vukmir, R.B. et al., 1995. Sodium bicarbonate may improve outcome in dogs with brief or prolonged cardiac arrest. *Critical care medicine*, 23(3), pp.515-22.

Abstract
Objective: Despite the absence of outcome evaluation, the use of sodium bicarbonate in cardiac arrest has declined based on advanced cardiac life-support guidelines. The effects of bicarbonate therapy on outcome in a canine model of ventricular fibrillation cardiac arrest of brief (5-min) and prolonged (15-min) duration were examined.
Design: Prospective, randomized, controlled trial.
Setting: Experimental animal laboratory in a university medical center.
Subjects: Thirty-two adult dogs, weighing 10 to 17 kg.
Interventions: The animals were prepared with ketamine, nitrous oxide/oxygen, halothane, and pancuronium. Ventricular fibrillation was then electrically induced and maintained in arrest for 5 mins (n = 12) or 15 mins (n = 20). Canine advanced cardiac life-support protocols were instituted, including defibrillation, cardiopulmonary resuscitation (CPR), and the administration of epinephrine (0.1 mg/kg), atropine, and lidocaine. The bicarbonate group received 1 mmol/kg of sodium bicarbonate initially, and base deficit was corrected to -5 mmol/L with additional bicarbonate, whereas acidemia was untreated in the control group. Cardiopulmonary values were recorded at intervals between 5 mins and 24 hrs, and the neurologic deficit score was determined at 24 hrs after CPR.
Measurements and Main Results: The treatment group received an additional 2 to 3 mmol/kg of bicarbonate in the early postresuscitation phase. Compared with controls, the bicarbonate group demonstrated equivalent (with brief arrest) or improved (with prolonged arrest) return of spontaneous circulation and survival to 24 hrs, with lessened neurologic deficit. The acidosis of arrest was decreased in the prolonged arrest group without hypercarbia. Improved coronary and systemic perfusion pressures were noted in the bicarbonate group with prolonged arrest, and the epinephrine requirement for return of spontaneous circulation was decreased.
Conclusions: The empirical administration of bicarbonate improves the survival rate and neurologic outcome in a canine model of cardiac arrest.

1. Level of Evidence – 3
2. Methodological quality – good (RCT but not blinded)
3. Magnitude of any observed effect – significant

4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supports
5. Outcome(s) assessed – A
6. Relevance to the question asked - v-fib 5 or 15 min; bicarb group received initial 1mmol/kg then corrected BE to -5; equal ROSC in 5 min; improved ROSC 15min

53: Vukmir, R.B. & Katz, L., 2006. Sodium bicarbonate improves outcome in prolonged prehospital cardiac arrest. *The American journal of emergency medicine*, 24(2), pp.156-61.

OBJECTIVE: This study evaluates the effect of early administration of an empirical (1 mEq/kg) sodium bicarbonate dose on survival from prehospital cardiac arrest within brief (<5 minutes), moderate (5-15 minutes), and prolonged (>15 minutes) down time. METHODS: Prospective randomized, double-blinded clinical intervention trial that enrolled 874 prehospital cardiopulmonary arrest patients managed by prehospital, suburban, and rural regional emergency medical services. Over a 4-year period, the randomized experimental group received an empirical dose of bicarbonate (1 mEq/kg) after standard advanced cardiac life support interventions. Outcome was measured as survival to emergency department, as this was a prehospital study. RESULTS: The overall survival rate was 13.9% (110/792) for prehospital arrest patients. There was no difference in the amount of sodium bicarbonate administered to nonsurvivors (0.859 +/- 0.284 mEq/kg) and survivors (0.8683 +/- 0.284 mEq/kg) (P = .199). Overall, there was no difference in survival in those who received bicarbonate (7.4% [58/420]), compared with those who received placebo (6.7% [52/372]) (P = .88; risk ratio, 1.0236; 0.142-0.1387). There was, however, a trend toward improved outcome with bicarbonate in prolonged (>15 minute) arrest with a 2-fold increase in survival (32.8% vs 15.4%; P = .007). CONCLUSION: The empirical early administration of sodium bicarbonate (1 mEq/kg) has no effect on the overall outcome in prehospital cardiac arrest. However, a trend toward improvement in prolonged (>15 minutes) arrest outcome was noted.
1. Level of Evidence – 6
2. Methodological quality – good (RCT)
3. Magnitude of any observed effect – neutral; trend toward improved survival with bicarb in prolonged arrect (P<0.007)
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – supports (I would call P<0.007 significant)
5. Outcome(s) assessed – B
6. Relevance to the question asked - Gave 1mEq/kg bicarb to 5 min, 5-15 min and >15 min pre-hosp arrest in addition to recommended ACLS

54: van Walraven, C. et al., 1998. Do advanced cardiac life support drugs increase resuscitation rates from in-hospital cardiac arrest? The OTAC Study Group. *Annals of emergency medicine*, 32(5), pp.544-53.

Abstract

Study objective: The benefit of Advanced Cardiac Life Support (ACLS) medications during cardiac resuscitation is uncertain. The objective of this study was to determine whether the use of these medications increased resuscitation from in-hospital cardiac arrest. **Methods:** A prospective cohort of patients undergoing cardiac arrest in 1 of 5 academic hospitals was studied. Patient and arrest factors related to resuscitation outcome were recorded. We determined the association of the administration of ACLS drugs (epinephrine, atropine, bicarbonate, calcium, lidocaine, and bretylium) with survival at 1 hour after resuscitation. **Results:** Seven hundred seventy-three patients underwent cardiac resuscitation, with 269 (34.8%) surviving for 1 hour. Use of epinephrine, atropine, bicarbonate, calcium, and lidocaine was associated with a decreased chance of successful resuscitation (P <.001 for all except lidocaine, P <.01). While controlling for significant patient factors (age, gender, and previous cardiac or respiratory disease) and arrest factors (initial cardiac rhythm, and cause of arrest), multivariate logistic regression demonstrated a significant association between unsuccessful resuscitation and the use of epinephrine (odds ratio .08 [95% confidence interval .04–.14]), atropine (.24 [.17–.35]), bicarbonate (.31 [.21–.44]), calcium (.32 [.18–.55]), and lidocaine (.48 [.33–.71]). Drug effects did not improve when patients were grouped by their initial cardiac rhythm. Cox proportional hazards models that controlled for significant confounders demonstrated that survivors were significantly less likely to receive epinephrine (P <.001) or atropine (P <.001) throughout the arrest. **Conclusion:** We found no association between standard ACLS medications and improved resuscitation from in-hospital cardiac arrest. Randomized clinical trials are needed to determine whether other therapies can improve resuscitation from cardiac arrest when compared with the presently used ACLS drugs.

1. Level of Evidence – 6
2. Methodological quality – good (prospective cohort humans)
3. Magnitude of any observed effect – none
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – neutral
5. Outcome(s) assessed – A, C
6. Relevance to the question asked - bicarb (and any ALS drugs) had no effect on survival in multivariate analysis

55: Weil, M.H. et al., 1985. Acid-base determinants of survival after cardiopulmonary resuscitation. *Critical care medicine*, 13(11), pp.888-92.

The acid-base and electrolyte conditions which favor survival were examined in 105 patients during and after CPR. There was a sharp decrease in survival when arterial pH exceeded 7.55 during the initial 10 min after initiation of CPR. Measurements made one hour after successful resuscitation also demonstrated an increase in mortality when pH exceeded 7.55. Arterial blood lactate also served as a sensitive quantitative indicator of prognosis, both during and one hour after successful CPR. The adverse effects of alkalemia were largely explained by increases in whole-blood bicarbonate, plasma sodium, and plasma osmolality after administration of sodium bicarbonate.

1. Level of Evidence – 6
2. Methodological quality – poor (retrospective human)

3. Magnitude of any observed effect – significant
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposes
5. Outcome(s) assessed – B
6. Relevance to the question asked - pH >7.55, increased whole blood bicarbonate correlated with decreased survival; author associates with bicarb administration

56: White, B.C. & Tintinalli, J.E., 1977. Effects of sodium bicarbonate administration during cardiopulmonary resuscitation. *JACEP*, 6(5), pp.187-90.

To study whether sodium bicarbonate given in cardiopulmonary resuscitation may produce life-threatening hyperosmolality or hypernatremia, arterial blood was analysed for blood gas, alcohol, blood urea nitrogen, electrolyte and osmolality. The blood was drawn after resuscitation in successful cases, and while effective massage and ventilation were being applied in unsuccessful resuscitations. Seven of the 17 resuscitations were successful. Serum sodium concentrations ranged from 135 to 154 with one exception and did not correlate with the amount of sodium bicarbonate administered. Arterial pH ranged from 6.38 to 7.71; only one patient had metabolic alkalosis. Serum osmolality ranged from 301 to 407. The data suggests a net increase in osmolality of 6 mOsm/50 mEq of sodium bicarbonate.
1. Level of Evidence – 6* cannot access
2. Methodological quality –
3. Magnitude of any observed effect –
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed –
5. Outcome(s) assessed – E= serum osmolality, Na+
6. Relevance to the question asked –

57: Wiklund, L. et al., 1997. Response of myocardial cellular energy metabolism to variation of buffer composition during open-chest experimental cardiopulmonary resuscitation in the pig. *European journal of clinical investigation*, 27(5), pp.417-26.

The aim of the present study was to investigate possible relationships in piglets between myocardial energy-related metabolites and intracellular electrolytes during open-chest cardiopulmonary resuscitation (OCCPR) supplemented by the administration of alkaline buffers with varying sodium content. Our hypothesis was that an increasing myocardial intracellular sodium content would decrease the intracellular energy stores. In addition to haemodynamics, acid-base and blood gas variables were analysed, and myocardial biopsies were collected before and during OCCPR as well as after the return of spontaneous circulation. After a period of 4 min of untreated ventricular fibrillation (VF). 25 piglets were randomly allocated to one of four groups: OCCPR with normal saline (n = 5); OCCPR with sodium bicarbonate (SB) (n = 7); OCCPR with Tris buffer mixture (TBM) (n = 7); and a totally untreated control group (n = 6). The results showed that 4 min of untreated VF almost eradicated creatine phosphate (CrP) and that the ATP/ADP ratio decreased to 1.5-2.0. During OCCPR with normal saline, the myocardial content of

CrP increased, whereas lactate, ATP and ADP levelled off and AMP decreased, causing an increased ATP/ADP ratio. The adenosine and inosine contents increased, whereas inosine monophosphate was unchanged at a low level, the adenosine and inosine contents being inversely correlated with the total content of adenine nucleotides. In both buffered groups, the increase in most energy-related metabolites (CrP, ATP, ADP, AMP and the ATP/ADP quotient) was less and in lactate more pronounced than in the group not being buffered, with no difference between the groups receiving SB or TBM. Although the intracellular potassium content was unaltered, the sodium, chloride and calcium concentration increased, more so in the group receiving SB. The intracellular content of sodium was correlated with that of calcium. Thus, buffering increased the myocardial AMP degradation during OCCPR by increasing the flux via the 5'-nucleotidase reaction, and SB increased the intracellular contents of sodium and calcium to a greater extent than did TBM.

1. Level of Evidence – 6
2. Methodological quality – good (RCT piglets)
3. Magnitude of any observed effect – significant - decreased
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposing
5. Outcome(s) assessed – E=myocardial energy metabolite levels
6. Relevance to the question asked - 4 min vfib followed by bicarb or tris. Energy metabolites decreased in both compared to no txt; increased intracellular Na, Cl- and Ca+ with bicarb compared to tris

58: Wiklund, L. et al., 1990. Effects of alkaline buffer administration on survival and myocardial energy metabolism in pigs subjected to ventricular fibrillation and closed chest CPR. *Acta anaesthesiologica Scandinavica*, 34(6), pp.430-9.

Nineteen anaesthetized piglets were investigated. After characterization and a stabilization period, ventricular fibrillation was induced by a transthoracic DC shock, after which a 10-min period of cardiopulmonary resuscitation (CPR) took place. CPR included manual chest compression and mechanical ventilation with pure oxygen. After 1 min of CPR an infusion of alkaline buffer was begun and was completed within 5 min. A total of 50 mmol of one of two different buffer solutions was given, either sodium bicarbonate (n = 6) or tris buffer mixture (n = 7). These two groups were compared with a third control group (n = 6) receiving the same volume of normal saline. After 8 min of CPR all animals were given 0.5 mg adrenaline i.v., and after 10 min DC shocks were used to return the heart to normal sinus rhythm. If this procedure was successful, the heart was rapidly (within 15 s) stopped again by another DC shock. Myocardial biopsies were then taken immediately in all animals. Successful CPR was more frequent in the animals given normal saline or tris buffer mixture and no effect was seen in the group given sodium bicarbonate. Survival was statistically correlated to low myocardial content of creatine phosphate and low base excess values in blood. Such parameters as myocardial content of ATP or ACP (adenylate charge potential) had no direct correlation to survival. Sodium bicarbonate induced significantly higher base excess and PCO2 values, while the tris buffer mixture seemed to have a greater alkalizing effect

intracellularly. We consider it probable that the poor results regarding survival after experimental CPR combined with a rapid infusion of sodium bicarbonate were a result of the excessive alkalosis created in combination with the higher resulting PCO2. Indirect evidence was given that a slightly alkaline pH also intracellularly supported critical reactions including ATPases essential for cellular survival.

1. Level of Evidence – 6* cannot access
2. Methodological quality – good (RCT piglets)
3. Magnitude of any observed effect – unclear - need article
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposing
5. Outcome(s) assessed – ROSC
6. Relevance to the question asked - tris v. bicarb v. saline 10 min closed-chest after vfib

59: Wiklund, L. et al., 1986. Kinetics of carbon dioxide during cardiopulmonary resuscitation. *Critical care medicine*, 14(12), pp.1015-22.

CO2 kinetics during CPR was investigated in 15 anesthetized piglets. BP, blood gases, and acid-base balance were monitored through catheters in the carotid artery and a central vein, as well as in cerebrospinal fluid. Cardiac arrest was induced by a transthoracic direct current shock. CPR was begun immediately by artificial ventilation and simultaneous external chest compressions. Epinephrine was administered after 8 min of CPR. One group (n = 5) of animals received no buffer treatment while another (n = 5) received an infusion of 75 mmol sodium bicarbonate and a third group (n = 5) received an equivalent amount of tris-buffer mixture. The results of these experiments, as well as previously described circulatory variables during CPR, were analyzed using a computer model describing the CO2 kinetics of the pig. Our main finding was that PaCO2 was positively correlated to cardiac output during CPR; improved cardiac output during CPR resulted in more efficient tissue CO2 elimination and was associated with increased survival rates. PaCO2 was also somewhat reduced by efficient alveolar hyperventilation. The arterial PCO2 and pH did not reflect the acid-base balance in peripheral tissues. During CPR, bicarbonate and tris-buffer mixture both quickly passed through the blood-brain barrier. When buffer treatment is indicated during CPR, a buffer which does not increase tissue PCO2 may be the drug of choice.

1. Level of Evidence – 6
2. Methodological quality – good
3. Magnitude of any observed effect – significant
4. Direction of support or otherwise for the question asked, according to the specific outcomes that have been assessed – opposing
5. Outcome(s) assessed – E=CSF pCO2
6. Relevance to the question asked - CSF pCO2 higher in bicarb group compared to saline or tris, lower in tris compared to saline