**Clinical question.**

In pediatric patients with cardiac arrest (pre-hospital [OHCA] or in-hospital [IHCA]) (P), does the use of calcium (I) compared with no calcium (C), improve outcome (O) (eg. ROSC, survival to hospital discharge, survival with favorable neurologic outcome)?

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

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

**Conflict of interest specific to this question**

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

**Search strategy (including electronic databases searched).**

**PubMed**
- "Calcium" [Mesh] AND “Heart Arrest” [Mesh]
- "Calcium Chloride" [Mesh] AND "Cardiopulmonary Resuscitation” [Mesh]
- "Calcium Chloride” [Mesh] AND “Heart Arrest” [Mesh]
- "Calcium Gluconate” [Mesh] AND “Heart Arrest” [Mesh]
- "Calcium Gluconate” [Mesh] AND “Cardiopulmonary Resuscitation” [Mesh]

1577 hits

after thinning, 21 papers

**American Heart Association EndNote Database**
- "Calcium” [Mesh] AND “Cardiopulmonary Resuscitation” [Mesh]
- "Calcium” [Mesh] AND “Heart Arrest” [Mesh]
- "Calcium Chloride” [Mesh] AND “Cardiopulmonary Resuscitation” [Mesh]
- "Calcium Chloride” [Mesh] AND “Heart Arrest” [Mesh]
- "Calcium Gluconate” [Mesh] AND “Heart Arrest” [Mesh]
- "Calcium Gluconate” [Mesh] AND “Cardiopulmonary Resuscitation” [Mesh]

0 hits to supplement PubMed search

**EMBASE**
- (heart arrest or cardiopulmonary resuscitation) AND (calcium OR calcium ion OR calcium chloride OR calcium glucoheptonate)

0 hits to supplement PubMed search

**Cochrane calcium search**
- 1. calcium
- 2. heart arrest
- 3. cardiopulmonary resuscitation
- 4. cardiopulmonary arrest
- 5. 2 or 3 or 4
- 6. 1 and 5

4 hits; none applicable

4 pulled by hand search of references

Nothing picked up on web of science search using major papers (clinical RCTs)

**State inclusion and exclusion criteria**

**Inclusion Criteria:**
- Article dealing directly with calcium and heart arrest.

**Exclusion Criteria:**
- Article not dealing directly with calcium or heart arrest.
- Article not adding evidenciary support to answer the clinical question (Editorial, review).
- Single case reports.
- Articles not fully available for analysis (Abstracts)

**Number of articles/sources meeting criteria for further review:** 21 articles; 1 LOE 2, 2 LOE 3, 1 LOE 4, 17 LOE 5
### Summary of evidence

#### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>1</th>
<th>2</th>
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<td>Kay, 1951 ABC</td>
<td>Cairns, 1991 E</td>
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#### Level of evidence

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  

*Italics = Animal studies*
### Evidence Neutral to Clinical question

<table>
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#### Level of evidence

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

- **Stiell, 1995 ABC**
- **Ornato 1985 E**
- **Niemann, 1999 E**
- **Urban, 1988 E**
- **Best, 1985 E**
- **Gando, 1988 AB**
- **Gando, 1990 E**
- **Steuven, 1985 ABC**
## Evidence Opposing Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
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</table>

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
Calcium is a highly relevant cation during myocardial impulse formation and contraction. Because of its physiological properties and initial evaluation in case reports, its use had been recommended during advanced cardiopulmonary resuscitation efforts. However, later reports of scientific evidence, mainly in canine models, started a controversy in its use, since most publications did not show any benefit regarding calcium use in heart arrest, and many even suggested that its supplementation could be harmful based on the risk of hypercalcemia. Several studies have also implicated intracytoplasmic calcium accumulation in the final pathway of cell death.

Keeping this in mind, in 2000, the American Heart Association (AHA) recommended that calcium should be used only in selected clinical scenarios, which are documented hypercalcemia, hypomagnesemia, hypocalcemia and calcium channel blocker overdose. The same guidelines even suggested that calcium should not be used since it could be harmful and had not proven effectiveness.

It was the objective of this review to evaluate the use of Calcium in pediatric heart arrest.

The review was started using papers that observed changes in calcium levels during cardiac arrest. 7 publications were found, including animal (Best, 1985; Cairns, 1991; Niemann 1999) and human (Gando et. Al. 1988, 1990, 1997 and Urban 1988) models. None included children in their study groups. Most of them concluded that a progressive state of hypocalcemia developed during heart arrest, except for Best's dog study that did not show the phenomenon. Two studies (Cairns 1991, Gando 1997) also showed a statistically significant correlation between the development of hypocalcemia and acidosis, reflected in a decrease in pH (Gando 1997) and lactate (Cairns 1991) levels. Another study in dogs (Niemann 1999) also showed that hypocalcemia could be associated with a progressive increase in potassium concentration. In spite of these three studies, no clear explanation for the decrease in calcium levels can be given, since all of them have important methodologic limitations. However, these studies do provide the basis to formulate the question whether hypocalcemia affect the resuscitation effort’s outcome and whether it should be treated in order to improve outcomes.

The first studies to evaluate the potential therapeutic benefits of calcium included mainly animal (dog) studies, in which cardiac arrest was induced in a wide variety of rhythms (Redding, 1983, Blecic 1985, Niemann 1985, and Niemann 1999). Most of them were small and had important methodologic problems, mainly regarding the statistic tests chosen for analysis, choosing parametric tests in which that condition was unlikely to be seen. Some studies did not even show the dogs’ basic characteristics, which made impossible to make comparisons between the groups evaluated. Most of them concluded that calcium had either no benefit or was potentially harmful during heart arrest, but no clear conclusion could be made after reviewing these experiments alone, since the evidence level they had and the methodological problems found during analysis.

There were some publications that were supportive for the use of calcium during heart arrest. The first one is an old case report of 4 pediatric heart arrests in which a successful outcome was obtained (Kay and Blalock, 1951). However, significant limitations exist in the quality of their reported data. First, all of the events recorded were intraoperative, and involved witnessed cardiopulmonary arrests in patients who had had a sternotomy. Second, there is no clear report regarding the rhythm each of the patients were in. Third, patients were treated using very high doses of epinephrine that was also administrated intracardially, and finally half of them had had transfusions before the arrest. All of these characteristics make this case report unsuitable for supporting the use of calcium in routine pediatric heart arrest. The are also two other studies that show that a progressive state of hypocalcemia develops during heart arrest (Gando 1997, Cairns 1991). Both of them are purely observational, Gando’s study a prospective cohort of 32 adult patients and Cairns’ study an experimental model in 9 adult dogs. Neither of them are suitable to support a recommendation for
calcium use during routine cardiopulmonary resuscitation, since they are both likely underpowered, do not include a pediatric population and Cairns’ study in dogs has important statistical errors regarding the choice of tests used that makes its results unreliable. Summarizing, no high-quality studies supporting calcium use could be found, and those that are available are not reliable enough to support a recommendation.

The majority of studies reviewed either showed no benefit (Pearson 1963, Ornato 1985, Stueven 1983, Stueven 1985, Stiell 1995) or potential harm (Walraven 1998) with the use of calcium during routine resuscitation efforts. The studies before 2000 gave the foundation to state that year AHA’s recommendation, withholding calcium use only to the abovementioned clinical scenarios. However, most of them have methodological limitations. None of them include pediatric population in the study groups, some do not test for potential confounding variables and others do not use the appropriate statistical tools for analysis. All of these limitations implied the need for further research before a new conclusion could be made.

After the 2000 AHA’s recommendation regarding calcium use, however, three pediatric studies were conducted that gave more insight regarding this matter. The first of them was conducted in 2006 (deMos et al., 2006), a retrospective cohort study of in-intensive care unit (ICU) pediatric heart arrest, including 91 children. The study evaluated survival and neurologic outcome through univariate a multivariate analysis, and showed a statistically significant association between calcium use and in-hospital mortality in univariate and multivariate analysis (Adjusted Odds Ratio - aOR- 5.4; 95%CI 1.1 - 25) amongst other important factors such as renal failure (aOR 6.1 95%CI 1.8 - 31) and being on epinephrine infusion before the arrest (aOR 9.5; 95%CI 1.5 - 62). Although retrospective, this publication represented the best available evidence to that date, since it is well designed, controls potentially confounding variables though regression analysis and uses appropriate statistical tools to make its conclusions. The authors however, do conclude that prospective analysis is still needed, considering the intrinsical limitations that retrospective studies have. If we also consider that logistic regression can be inaccurate calculating the aORs when the frequency of the outcome event exceeds 10% of cases, the need for further study becomes more patent.

Two years later, Srinivasan el al. published a cohort study that prospectively evaluated calcium use during in hospital pediatric cardiopulmonary resuscitation (Srinivasan, 2008). This study was a large multicenter prospective cohort study that only included 1477 pediatric patients, evaluating survival and neurologic outcome at hospital discharge. However, it must be considered that in its methods is stated that neurologic outcome was evaluated through chart review, therefore in a retrospective manner. This study showed that calcium use was still a frequent practice in routine cardiopulmonary resuscitation efforts, reaching 45% of cases, in spite of the 2000 AHA’s recommendation. Also through multivariate analysis (logistic regression), and therefore adjusting for potentially confounding factors, calcium was still associated with worse overall outcome, including survival to hospital discharge (aOR 0.6; CI95% 0.5 - 0.9) and neurologic outcomes (aOR 0.6; CI95% 0.4 - 0.8). Calcium was more likely to be used in pediatric (OR 1.9; CI95% 1.4 - 2.6), ICU patients (OR 1.7; CI95% 1.2 - 2.4), patients more than 15 minutes in heart arrest (OR 2.2; CI95% 1.6 - 3), when the first documented rhythm was asystole (OR 1.3 CI95% 1.1 - 1.8) and amongst many other arrest medications, which shows that generally it tends to be used in more critically ill patients. However, logistic regression controls these variables and makes calcium’s association with worse overall outcomes valid. Srinivasan’s study represents the best available evidence to date that shows that calcium should not be used during routine cardiopulmonary resuscitation efforts.

A third study by Meert et al. also confirmed the association of calcium with worse outcomes, particularly survival to hospital discharge (Meert 2009). The study was a retrospective cohort conducted in 15 different centers; a total of 353 children were included. It showed that calcium was a commonly used therapy, since it was prescribed in more than half of cases (51.9%). Through multivariate logistic regression analysis it also showed that calcium was independently associated with in-hospital mortality (aOR: 2.26; 95%CI: 1.29 - 3.96, p<0.01). The study does have its limitations, mainly regarding the inclusion and exclusion criteria used and its retrospective design, but it still provides a reasonable basis to recommend the avoidance of calcium during routine resuscitation efforts.

After considering all of the abovementioned comments, the following conclusions can be made:
1.- Calcium use in routine cardiopulmonary resuscitation is associated with worse survival and neurologic outcome.

2.- In spite of the 2000 AHA Guidelines regarding pediatric heart arrest, calcium is still widely used in resuscitation efforts.

3.- Most of the scientific evidence available comes from studies that are neither prospective nor randomized, and do not include pediatric population in its study groups. However, we consider that it would ethically questionable to conduct a randomized, controlled trial with the antecedents given to date. Considering this, Srinivasan’s cohort represents an ideal state of balance between ethics and evidence-based medicine, since it allows us to make a recommendation with a reasonable level of evidence through a purely observational study.

4.- Our efforts should be directed toward reinforcing the 2000 AHA’s recommendation, restricting calcium use to the following clinical scenarios: hypercalemia, hypomagnesemia, hypocalcemia and calcium channel blocker overdose.

**Acknowledgements:**

Dr. Felipe Martínez for its statistical assistance during the review of the available evidence.

Dr. Sergio Pesutic for helping during the review of the available evidence.
Citation List


Study Characteristics
- Experimental study in 15 adult dogs.
- Interventions between groups asymmetrical. One group used a mechanical resuscitator rather than standard cardiac compressions.
- Calcium administrated when EMD was achieved (0.5 - 1g).
- Statistics used: Hotteling’s T Test.

Main Findings:
- No change in ionized calcium levels over the course of prolonged resuscitation (p = 0.18).
- 3/4 dogs treated with calcium chloride developed severe hypercalcemia.

Study Limitations
- Not a Pediatric / Non asphyxial model.
- Small sample size, likely underpowered.
- Hotteling’s T Test (MANOVA) without testing for data distribution.
- Interventions in both groups asymmetrical.
- High dose epinephrine used in both dogs.

LOE: 5
Quality Level: Poor
Supporting / Neutral / Opposing: Neutral

Study Characteristics
• Experimental model examining the benefit of calcium in CPR in a canine model.
• Calcium was tested only in after VF-induced EMD (non-hypoxic)
• Placebo controlled (Dextrose, Epinephrine), fixed dose only (not in Weight / Kg)
• Outcome measures: ROSC, Death; Post - resuscitation mean arterial pressure, PO₂, PCO₂, pH, HCO₃⁻
• Statistics used: Mean +/- DS, Student’s T Test for paired samples.

Main Findings:
• Calcium is as effective as placebo in achieving ROSC.
• Post resuscitation MAP was lower in CaCl₂ group than in epinephrine group. Equivalent to placebo.

Study Limitations
• Experimental study in dogs, not a pediatric population.
• Small sample size.
• Student’s T Test not the optimal statistical tool to use without testing for data distribution and variances.
• Qualitative data are not tested (ROSC / Death) with Fisher’s Exact Test, for example.
• Not an hypoxic model.

LOE: 5
Quality Level: Poor
Supporting / Neutral / Opposing: Opposing

**Study Characteristics**
- Experimental observational study in 9 adult dogs.
- Rhythm: Induced Asystole or PEA
- Interventions between groups asymetrical. One group used a mechanical resuscitator rather than standard cardiac compressions.
- Calcium administrated when EMD was achieved (0.5 - 1g).
- Statistics used: ANOVA, Student’s T for paired samples, Linear regression.

**Main Findings:**
- Calcium decreased with resuscitation efforts.
- Lactate increased during resuscitation efforts.
- Correlation between calcium and lactate levels ($r = -0.72$, $p < 0.001$); does not inform $r$ square.

**Study Limitations**
- Not a Pediatric / Non asphyxial model.
- Small sample size, likely underpowered.
- ANOVA / Student’s T used without testing for sample’s distribution. Normal distribution highly unlikely.

**LOE:** 5

**Quality Level:** Poor

**Supporting / Neutral / Opposing:** Supporting

Study Characteristics
- Retrospective cohort study of in-ICU-pediatric heart arrest.
- Inclusion criteria: <18 years, heart arrest during ICU stay.
- Modified definitions of heart arrest criteria.
- Only the first episode analyzed in those patients that had multiple cardiac arrests.
- Outcomes: Survival (at ECMO/ROSC, 24 hours after CPR, ICU stay, Hospital stay, 12 months). Neurologic status evaluated through the PCPC and POPC scores.
- Incomplete data was assumed to be normal.
- Statistics used: Wilcoxon Rank Sum Test, Ji Square, Fisher’s exact test. Logistic Regression. Linear regression for POPC / PCPC scores with heart arrest duration.

Main Findings: (Only those relevant to clinical question selected)
- Calcium associated with in-hospital mortality in univariate and mutivariate analysis (MR-OR: 5,4 CI95% = 1,1 - 25)
- Prospective analysis needed.

Study Limitations & Characteristics
- Pediatric population
- Statistic methods are adequate, though with 91 patients it is likely that a parametric distribution of data could be found. Therefore, testing for data distribution and variances could have validated the use of Student’s T Test, which is more accurate than the Mann - Whitney U test.
- Multivariate Logistic Regression is tool that helps standardizing the surviving and nonsurviving groups. However, it can be inaccurate calculating the OR since death is an event that occurs in more than 10% of patients in heart arrest.

LOE: 3
Quality Level: Good
Supporting / Neutral / Opposing: Opposing
Gando S., Igarashi M. et Al. **Ionized hypocalcemia during out-of-hospital cardiac arrest and cardiopulmonary resuscitation is not due to binding by lactate.** Intensive Care Med 23(12) (1997) 1245-50

**Study Characteristics**
- Prospective cohort study, OHCA / IHCA, 32 patients, 14 ROSC, 18 died.
- Inclusion criteria: >16 years of age
- Exclusion criteria: >90 years of age, trauma, hypothermia, terminal illness, positive death signs.
- No calcium chloride was used.
- Statistics used: Mann Withney U, Ji square, Kruskall Wallis for variance, Wilcoxon signed ranks test, linear regression.

**Main Findings:**
- All ER patients had hypocalcemia (1,09)
- Hypocalcemia worsened over time. Significant correlation was observed ($r^2 = -0,125$, $p=0.047$).
- No changes in lactate concentration over time.
- Significant correlation in survivors between calcium and pH, but not with bases.

**Study Limitations & Characteristics**
- Non - Pediatric population
- Small sample, statistics underpowered but the choice of tests seems adequate.
- Not assessing the use of calcium in CPR.
- Patient characteristics shown, however no rhythm characterization data is provided.

**LOE:** 5
**Quality Level:** Fair
**Supporting / Neutral / Opposing:** Supporting

Study Characteristics
- Observational study in 22 patients.
- Excluded: Pediatric and trauma patients.
- Evaluated changes in calcium in arterial and mixed venous blood.
- Statistics Used: Student’s T for paired samples test, Ji Square, F - Test (Fisher - Snedecor test)
- Patients analyzed by groups receiving and not receiving calcium. Further division in surviving or dead patients after this one was made.

Main Findings:
- Hipocalcemia increased with CPR’s duration.
- No difference between arterial and venous calcium.

Study Limitations
- Not a Pediatric population.
- Small sample size, likely underpowered.
- Student’s T used without testing for sample’s distribution. Normal distribution highly unlikely.
- Not clear which statistical tool was used in each case.

LOE: 5
Quality Level: Poor
Supporting / Neutral / Opposing: Neutral

**Study Characteristics**
- Observational study in 30 patients.
- Excluded: Pediatric and trauma patients.
- 11 Patients received Calcium Chloride (6.6mg/Kg)
- Statistics Used: Student’s T Test, Ji Square, F - Test (Fisher - Snedecor test)
- Patients analyzed by groups receiving and not receiving calcium. Further division in surviving or dead patients after this one was made.

**Main Findings:**
- Hypocalcemia was present in all patients.
- All transportation times were deemed to be low.
- Calcium - treated patients didn’t have any significant difference in their resuscitation success rate.

**Study Limitations**
- Not a Pediatric population.
- Small sample size, likely underpowered.
- Student’s T used without testing for sample’s distribution or variances. Normal distribution highly unlikely.
- Patient characteristics not shown.
- Correlation test used, not stated in methods?

**LOE:** 5
**Quality Level:** Poor
**Supporting / Neutral / Opposing:** Neutral

Study Characteristics
• Retrospective 24-month observation period (480 patients), evaluating ROSC in patients that received calcium chloride.
• Subgroup randomly selected of 200 patients for further analysis, because of “technical difficulties in analyzing such a large bulk of material”
• Adult patients only.
• Interventions differed according to initial rhythm (protocol shown), calcium was a “last resort” measure.
• Calcium use was not standardized. Mean dose of 900mg, range 400 - 1000.
• Statistics Used: Not Shown.

Main Findings:
• 27/480 patients responded to calcium, all in EMD.
• Main rhythm in subset of patients: EMD, VF was the most uncommon rhythm.

Study Limitations
• Not a Pediatric population.
• Patients not analyzed for confounding variables / No control group.
• Calcium dose not standardized.
• Statistics used not shown.
• Calcium used only as a “last resort” measure.

LOE: 5
Quality Level: Poor
Supporting / Neutral / Opposing: Opposing

Study Characteristics
• 4 Pediatric intraoperative cardiac arrests.

Main Findings:
• Calcium chloride effective in restoring ROSC in these patients.

Study Limitations
• Case series, evidence level too low to make a recommendation.
• Intraoperative arrests, drugs delivered intracardially.
• No statistical comparisons.
• Not clear what rhythm was present at each time.
• Transfusion given in 2 cases.

LOE: 4
Quality Level: Poor
Supporting / Neutral / Opposing: Supporting

Study Characteristics

- Multicenter retrospective study of in-hospital cardiac arrests in 15 children’s hospitals.
- Included: Patients between 1 day and 18 years of age who had cardiac arrest and ROSC/ECMO for at least 20 consecutive minutes. 353 patients were included. These criteria represent patients who would potentially be eligible for a randomized trial of the effect of clinical hypothermia on neurobehavioral outcomes.
- Excluded: NICU Arrests, Arrests during cardiac surgery, out-of-hospital arrests. Patients with less than 1 minute of CPR were also excluded, as were those without ROSC.
- Only the first event was recorded.
- Uniform database, investigators were trained in its use. Data monitoring was performed.
- Statistics used: Chi-square, Fisher’s Exact Test, Wilcoxon’s Rank-Sum Test, Cochrane - Armitage Test. Logistic Regression to identify variables that were associated with in hospital mortality. The logistic regression model was predefined for certain clinical variables, such as age, gender and first documented arrest rhythm, regardless of statistical significance. Forward stepwise selection was then applied to create the final model. Three different models were created: the first containing only variables known before and during the arrest, the second including variables known in the 12 hours postarrest, and the third excluding ECMO from analysis.

Main Findings:

- 172 (48.7%) patients survived until hospital discharge
- Calcium was more likely to be used in nonsurviving patients.
- Calcium was used in 174 patients (51.9%).
- Initiation of CPR was most often immediate with the first epinephrine dose usually being given within 1 to 2 mins of the start of arrest.
- In the second logistic regression model, calcium during the arrest was independently associated with in hospital mortality (OR: 2.26; 95%CI: 1.29 - 3.96, p<0.01)

Study Limitations

- Pediatric model with a reasonable sample size.
- Retrospective, therefore prone
- Inclusion criteria designed for a future randomized controlled trial, therefore not specifically designed to evaluate risk factors in pediatric heart arrest.
- Logistic regression models were used with combined clinical / statistical criteria. Variable selection, however, seems appropriate. It should also be considered that multivariate logistic regression can be inaccurate calculating the OR since death is an event that occurs in more than 10% of pediatric heart arrest patients.
- Conclusions regarding neurologic outcomes should not be used for comparison with other studies because of the inclusion/exclusion criteria.

LOE: 3
Quality Level: Fair
Supporting / Neutral / Opposing: Opposing

**Study Characteristics**

- Experimental model examining the benefit of calcium gluconate in canine post countershock heart arrest.
- Calcium was tested only when there was a failure to obtain an arterial pressure despite induced ventricular defibrillation (pacemaker), and was injected in the right ventricle.
- Epinephrine was given only in cases where the abovementioned measures failed to achieve ROSC.
- Myocardium studied through necropsy in four of the animals with samples obtained 20 min after ROSC. All received both calcium and epinephrine.
- Outcome measures: ROSC, Death; Aortic / RA and coronary perfusion pressure (Ao - RA) previous and after drug admin,
- Statistics used: Mean +/- DS, Student’s T Test for paired samples, Fisher’s Exact Test.

**Main Findings:**

- No difference for calcium in the mean Ao pressure previous and after CaCl$_2$.
- Epinephrine increased Ao and coronary perfusion pressures.
- No benefit for the use of calcium in heart arrest.

**Study Limitations**

- Experimental study in dogs, not a pediatric population.
- Small sample size.
- Student’s T Test not the optimal statistical tool to use without testing for data distribution and variances.
- Induced Post countershock arrest, non asphyxial.

**LOE: 5**

**Quality Level: Poor**

**Supporting / Neutral / Opposing:** Opposing

Study Characteristics
- Experimental animal study in dogs.
- Statistics used: ANOVA, Dunett’s T Test for multiple range comparisons.
- Not assessing calcium use, only testing for hypocalcemia and hyperkalemia.

Main Findings:
- Progressive increase in potassium during heart arrest.
- Decrease in calcium concentration.
- Successfully reanimated animals did not show any electrolyte imbalances.

Study Limitations
- Not a Pediatric population.
- Small sample size.
- ANOVA used without testing for data distribution.

LOE: 5
Quality Level: Fair
Supporting / Neutral / Opposing: Neutral

Study Characteristics
• Prospective study of 83 adults.
• Objective: Evaluate ability of countershock of converting what initially appeared on the ECG as asystole
• Drugs used according to standard ACLS protocol: Epinephrine, bicarbonate, atropine, CaCl2.
• Included: >17 years of age, Non - Traumatic arrest.
• Statistics Used: Ji Square / Student’s T

Main Findings:
• Epinephrine, atropine, CaCl infrequently changed rhythm.
• Countershock was statistically more useful in achieving this.

Study Limitations
• Not a Pediatric population.
• Patient characteristics shown, but insufficient. There is no information about initial comorbidities.
• Testing for distribution and variances highly desirable, borderline sample size.
• Not designed to evaluate calcium chloride’s effect on survival and neurologic outcome.

LOE: 5
Quality Level: Fair
Supporting / Neutral / Opposing: Neutral
Redding, JS, Haynes RR, et al. **Drug Therapy in resuscitation from electromechanical dissociation.**

**Study Characteristics**
- Experimental model examining the benefit of calcium gluconate in canine heart arrest.
- Asphyxial model.
- 4 Groups receiving: Isotonic Saline 5ml / Atropine 0.5mg / 500mg CaCl\(_2\) / methoxamine 20mg.
- Epinephrine was given only in cases where the abovementioned measures failed to achieve ROSC.
- Myocardium studied through necropsy in four of the animals with samples obtained 20 min after ROSC. All received both calcium and epinephrine.
- Outcome measures: ROSC, Death; Aortic / RA and coronary perfusion pressure (Ao - RA) previous and after drug admin,
- Statistics used: Mean +/- DS, Student’s T Test for paired samples, Fisher’s Exact Test.

**Main Findings:**
- Non significant increase in ROSC when compared to isotonic saline.

**Study Limitations**
- Experimental study in dogs, not a pediatric population.
- Small sample size.
- Statistic methods used not shown.
- No comparison between the 4 groups.

**LOE:** 5  
**Quality Level:** Poor  
**Supporting / Neutral / Opposing:** Opposing
Redding S, Pearson J. **Evaluation of Drugs for Cardiac Resuscitation.** Anesthesiology 24:2 (1963) 203 - 207

**Study Characteristics**
- Experimental study in 110 dogs.
- 11 groups. 1 - 7 received oxygen + CPR and different drugs (epinephrine, isoproterenol, phenylephrine, calcium chloride; 200mg) Groups 8 - 11 received one shock and similar medications intracardially.
- Statistics used: Not shown.

**Main Findings:**
- Calcium chloride significantly less effective than epinephrine.

**Study Limitations**
- Not a Pediatric population, asphyxial model.
- Dogs not compared for significant differences.
- High dose calcium used.
- Statistics used not shown.

**LOE:** 5  
**Quality Level:** Poor  
**Supporting / Neutral / Opposing:** Opposing.

Study Characteristics
• Large (1477; 659 receiving Calcium) prospective cohort multicenter study (167 hospitals)
• Inclusion criteria: <18 years of age, center providing data >6 months, first heart arrest (index)
• Exclusion criteria: OHCA, NICU / Delivery room arrests / DNR / arrests resolved by implantable defibrillator / cardioverter.
• Outcome: Survival to hospital discharge, event survival, neurologic outcome (PCPC). Neurologic outcome was retrospectively assessed.
• Statistics used: (STATA 8): Wilcoxon rank - sum, Ji square, logistic regression with OR.

Main Findings:
• Calcium use is a common practice despite AHA recommendations (45% cases).
• Calcium is more likely to be used in pediatric facilities and in critically ill patients.
• After adjusting for confounding factors, calcium was still associated with a worse outcome overall (worse survival to discharge and neurologic outcome)
• In settings of metabolic/electrolyte disturbances was not associated with worse outcome.

Study Limitations & Characteristics
• Pediatric population, large sample size.
• Mortality outcome was prospectively evaluated, however neurologic outcome was not.
• Statistics used seem limited for this sample size. Evaluation of sample’s distribution and variances could have validated Student’s T test for example.
• Control of confounding variables through logistic regression, which can be inaccurate when the occurrence of the clinical event exceed 10% of the studied population.

LOE: 2 for survival / 3 for neurologic outcome
Quality Level: Good
Supporting / Neutral / Opposing: Opposing

Study Characteristics
• Prospective cohort study, secondary analysis from a clinical trial.
• 650 patients enrolled in a previously reported controlled clinical trial (sample of 529)
• Exclusion criteria: <16 years of age, terminal illnesses, >15 mins to CPR, acute trauma.
• Statistics used: Ji square, Student’s T test, Cox proportional hazards model, multivariate logistic regression.

Main Findings:
• Calcium not associated with improved resuscitation outcome or discharge in univariate and multivariate analysis.
• No association between initial resuscitation and specific drug administration when analyzed according to cardiac rhythm.

Study Limitations
• Not a Pediatric population.
• Student’s T used without testing for data distribution and variances.
• Study not primarily designed to test whether calcium is beneficial or detrimental in resuscitation.

LOE: 5
Quality Level: Fair
Supporting / Neutral / Opposing: Neutral
Stueven H et Al. **Lack of Efectiveness of Calcium Chloride in Refractory Asystole.** Ann Emerg Med 14 (1985); 630 - 632

**Study Characteristics**
- Prospective study, 73 patients, non randomized, double blinded.
- Objective: Test whether calcium chloride is useful in refractory Asystole.
- Standardized doses of 500mg to patients in asystole were given (could have been in any kind of rhythm before), after receiving CPR, epinephrine, oxigen and bicarbonate.
- Excluded: Pediatric, Trauma, Poisoning, previous dose of Calcium Chloride, unable to secure airway or intravenous access.
- Statistics Used: Ji Square / Fisher’s Exact Test.

**Main Findings:**
- No patient that received calcium survived to hospital discharge.
- No significant difference between groups.

**Study Limitations**
- Not a Pediatric population.
- Patient characteristics not shown between groups not shown, not tested for significant differences.
- Underpowered (sample size of minimum 600 patients required)

**LOE:** 5  
**Quality Level:** Poor  
**Supporting / Neutral / Opposing:** Neutral

Study Characteristics
• Retrospective study, 718 adult patients, only those in EMD (81) and Asystole (129) analyzed.
• Statistics Used: Ji Square / Fisher’s Exact Test, Student’s T Test

Main Findings:
• 105 patients received calcium / 24 did not. Resuscitation rate: 8% / 33% p<0.002)
• Both groups controlled with univariate analysis, no statistically significant variables detected.
• No patient that received calcium survived to hospital discharge.
• No significant difference

Study Limitations
• Not a Pediatric population.
• Calcium dose not standarized nor stated.
• Multivariate analysis would have been highly desirable (logistic regression). Parametric distribution likely, but would also have been desirable to test for parametric distribution of data and variances of quantitive data.
• Control groups not designed to function as such. These groups existed because of clinical freedom in the indication of Calcium.

LOE: 5
Quality Level: Fair
Supporting / Neutral / Opposing: Opposing

**Study Characteristics**
- Observational study of 12 patients that had an out-of-hospital cardiac arrest. All received calcium, in doses that ranged from 500mg to 1000mg.
- OHCA patients had their samples obtained in a “brief time”. Calcium levels were not corrected for acidosis.
- Control group was a group of 10 patients who had an in-hospital cardiac arrest (ICU, Surgical floor).
- Patient characteristics shown in table 1, but not tested for statistically significant differences between groups.
- Statistics Used: Student’s T Test, Linear Regression.

**Main Findings:**
- High prevalence of hypocalcemia in heart arrest.
- No difference in calcium levels in patients that died or survived.
- More evidence needed.

**Study Limitations**
- Non pediatric population
- Small sample size.
- Calcium dosage not standardized.
- Statistic methods used not optimal for sample size. Non - parametric analysis should have been used with Mann - Whitney U test instead of Student’s T Test.
- No comparison between the two groups in table 1.

**LOE: 5**
**Quality Level: Poor**
**Supporting / Neutral / Opposing: Neutral**

Study Characteristics
• Prospective cohort study (773 patients), secondary analysis from a multicenter randomized trial.
• Exclusion criteria: <16 years, terminal illness, without basic CPR for more than 15 mins, acute trauma or exanguination, recent sternotomy, arrest in the operating, delivery or recovery rooms, not true cardiac arrest. Delay in receiving arrest drugs.
• Drugs given after ROSC were not evaluated.
• Outcome: Survival (after 1 hour).
• Statistics used: Ji square, Student’s T Test, Multivariate logistic regression (potentially confounding variable considered at significance level of 90%), Cox proportional Hazards model.

Main Findings:
• All drugs used in reanimation associated with worse outcome.

Study Limitations
• Not a Pediatric population.
• Student’s T test used without testing for data distribution and variances.
• Confidence limit used: 90% for univariate analysis (p values of 0,06 are deemed significant).
• Rhythm comparison between patients was done through a separate logistic regression for each rhythm.

LOE: 5
Quality Level: Fair
Supporting / Neutral / Opposing: Opposing