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Original Article

Current Practice of Calcium Use During Cardiopulmonary Bypass Weaning: Results of an International Survey

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Objectives: To describe international practices on the use of calcium salts during cardiopulmonary bypass (CPB) weaning in adult cardiac surgery patients.
Design: Multiple-choice survey on current practice of CPB weaning.
Setting: Online survey using the SurveyMonkey platform.
Participants: Departments of cardiac anesthesiology worldwide.
Interventions: None.
Measurements and Main Results: Out of 112 surveys sent, 100 centers from 32 countries replied. The majority of centers (88 of 100 = 88%) administer calcium salts intraoperatively: 71 of 100 (71%) are using these drugs for CPB weaning and 78 of 100 (78%) for correction of hypocalcemia. Among the 88 centers that use calcium salts intraoperatively, 66% (58 of 88) of respondents use calcium chloride, 22% (19 of 88) use calcium gluconate, and 12% (11 of 88) use both drugs. Calcium salts are routinely used during normal (47 of 71 centers = 66%) and difficult (59 of 71 centers = 83%) weaning from CPB. Doses of 5 to 15 mg/kg during termination of CPB were used by 55 of 71 centers (77%) either by bolus (39 of 71, 55%) or over a time period longer than 1 minute (32 of 71 = 45%). Norepinephrine is the most commonly used first line vasopressor or inotropic agent used to support hemodynamics during termination of CPB in 32 out of 100 centers (32%), and calcium is the second one, used by 23 out of 100 centers (23%).

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Conclusion: This survey demonstrates that the majority of cardiac centers use calcium in adult patients undergoing cardiac surgery, especially during weaning from CPB. There is variability on the type of drug, dose, and modality of drug administration.

Key Words: weaning from cardiopulmonary bypass; calcium; international survey; anesthesia; intensive care; cardiac anesthesia

WEANING from cardiopulmonary bypass (CPB) in patients undergoing cardiac surgery is considered one of the most critical moments during the procedure. Rapid restoration of normal cardiovascular function is necessary to prevent postoperative complications. Evidence indicates that 10 to 45% of patients are difficult to wean from CPB.[1-3] Even if there is no widely accepted definition of what is "difficult weaning from CPB," the dose of inotropes and vasopressors required during weaning is generally used for this purpose; high doses of vasoactive or inotropic agents (vasoactive-inotropic score >10) are a mark of difficult CPB weaning and are associated with high mortality in cardiac surgery.[4] Various drugs, such as catecholamines, phosphodiesterase-3 inhibitors, calcium sensitizers, and calcium salts are used to support hemodynamics during weaning from CPB.[5,6] Although all these drugs can effectively improve hemodynamics, serious side effects significantly limit their use.[7]

Calcium salts are often used to support hemodynamics during CPB weaning. The rationale for calcium administration in this setting comes from the results of several small studies that showed an increase in cardiac index, stroke volume, and mean arterial pressure when this drug was administered immediately after CPB.[8,9] On the other hand, risk of systemic side effects of calcium salts, such as the "stone heart" phenomenon, pancreatic injury, and inhibition of inotropic effects of catecholamines remain largely under recognized. Unfortunately, no high quality evidence exists regarding clinical efficacy and safety of calcium administration during weaning from CPB. Published studies carry significant limitations because of a small sample-size and assessment of surrogate endpoints.[10] There is no recent data on the use of calcium by cardiac anesthesiologists during weaning from bypass. Whether calcium salts should be administered during weaning for CPB has been a matter of debate for more than 20 years.[11,12]

In order to better understand current clinical practice, the authors conducted an international survey on calcium use during weaning from CPB in adult patients undergoing cardiac surgery.

Methods

The authors developed a survey to assess international practice on the use of calcium salts during weaning from CPB in adult patients (Supplementary Appendix). Survey design was similar to previous surveys performed in the cardiac anesthesia or intensive care setting.[13-17] This survey was tested preliminarily for ambiguity and applicability by colleagues of the senior author's department who were not involved in the development of the survey. The authors investigated demographic data (including respondent country, name, and type of the hospital, in addition to the number of surgeries and cardiac intensive care unit beds), indications, type of the drug, dosages, and mode of calcium administration and first-line inotropic or vasopressor drug used for CPB weaning. This survey was located on a web-based SurveyMonkey platform (Palo Alto, CA) and was opened for responses from March 20, 2019 to June 20, 2019.

An invitation letter by e-mail with the description of the purpose of the survey and hyperlink to the survey was sent to colleagues worldwide by e-mail. If no response was obtained, a second reminder e-mail was sent 2 weeks later. Social media was not used to advertise and distribute the survey. Only one response representing current practice was allowed from each hospital. If more than one answer was received from the same hospital, the head of the department was contacted to complete the survey, and her or his answers were considered for the analyses. Because of the nature of this survey, categorical data were analyzed and presented as percentages and absolute frequencies. No ethical committee approval was requested.

Results

The survey was sent to 112 centers and 100 hospitals from 32 countries responded, leading to a response rate of 89%, with the highest number of responses (n = 16) from the United States of America (Fig 1). Eighty-three percent (83 of 100) of responders were from university and academic hospitals, and 17% were from nonacademic hospitals. The number of adult cardiac surgery procedures under CPB varied from 50 to 5,500 per year (Supplementary Appendix: Table S1) with 48% (48 of 100) of hospitals performing 500 to 1,000 surgeries. The number of cardiac intensive care unit beds ranged from 4 to 80, with 45% (45 of 100) of hospitals having 10 to 20 beds (Supplementary Appendix: Table S1).

The vast majority of centers (88 of 100 = 88%) administer calcium salts intraoperatively as part of their clinical routine. Calcium salts are used for correction of hypocalcemia in 78 out of 100 hospitals (78%), for CPB weaning in 71 of 100 hospitals (71%), after transfusion of blood components in 54 of 100 hospitals (54%), and for optimization of hemostasis in 33 of 100 centers (33%). Only 3 centers (3 of 100, 3%) did not routinely measure calcium intraoperatively.

Among the 88 centers using calcium salts intraoperatively, 58 out of 88 (66%) use calcium chloride, 19 of 88 (22%) use calcium gluconate, and 11 of 88 (12%) use both of them (Fig 2).

Among the 71 centers that use calcium for CPB weaning, 47 out of 71 centers (66%) widely use (>50% of cases) calcium salts during normal CPB weaning and 59 of 71 centers (83%)

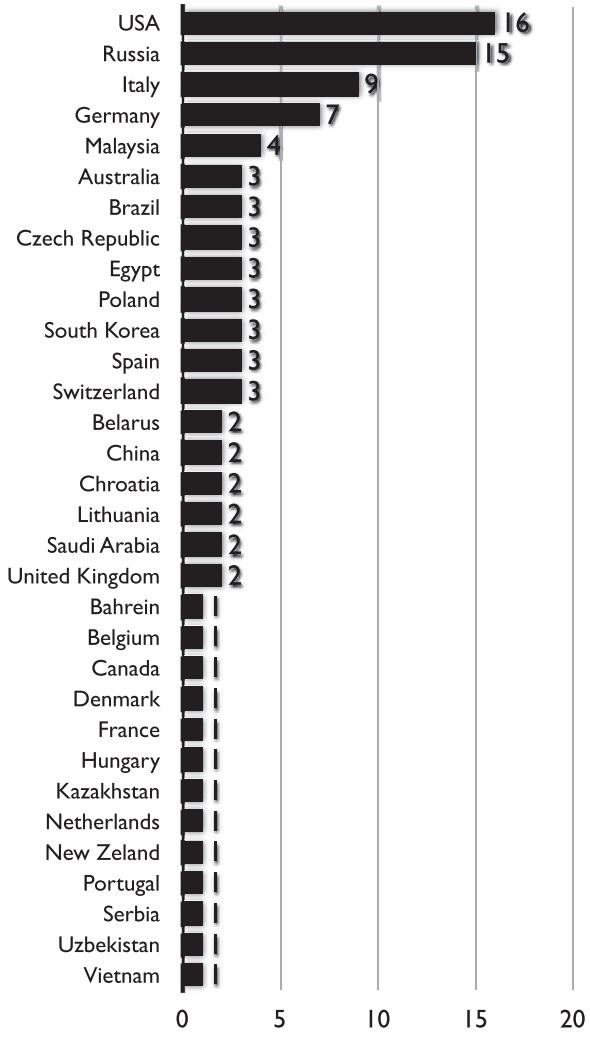

Fig 1. Number of hospitals participating to the survey for each country (total 100 hospitals from 32 countries).

widely use calcium salts during difficult weaning from CPB (Supplementary Appendix: Table S1).

The dose of calcium used during termination of CPB ranges from less than 5 mg/kg to more than 15 mg/kg with 25 out of 71 (35%) of centers using 5 to 10 mg/kg and 30 of 71 (42%) centers using more than 10 to 15 mg/kg (Fig 3) given by bolus or slow bolus (39 of 71 = 55% and 32 of 71 =45%,

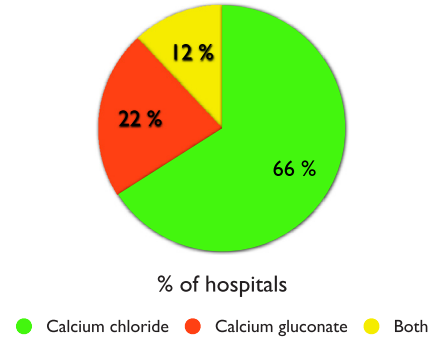

Fig 2. Types of calcium salts used by hospitals (among 88 centers that use calcium salts intraoperatively).

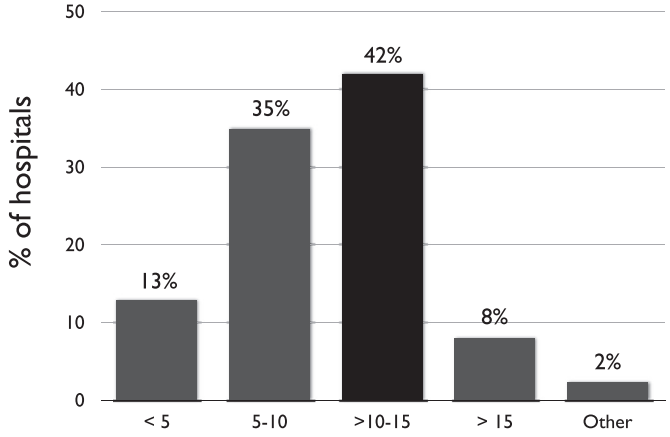

Fig 3. Total dose (mg/kg) of calcium used during cardiopulmonary bypass weaning.

respectively), with slow bolus indicating that the drug is given over a time period longer than 1 minute.

Norepinephrine is the most widely used first-line (used by 32 out of 100 centers [32%]) vasoinotropic drug to support hemodynamics during weaning from CPB, and calcium is the second (used by 23 out of 100 centers [23%]) (Fig 4).

Discussion

This international survey showed that even without the support of evidence-based medicine calcium salts are widely administered in adult patients undergoing cardiac surgery under CPB. The majority of centers (78 of 100 = 78% of responders) use calcium salts to correct hypocalcemia and to improve hemodynamics (71 of 100 = 71% of responders) during either normal (47 of 71 = 66% of responders) or difficult (59 of 71, 83%) CPB weaning and even as a second-line drug (23 of 100 = 23% of responders).

Daily practice and limited published studies provide evidence that administration of calcium salts briefly improves cardiac index and blood pressure in patients undergoing cardiac surgery. Even if there is no data on the effect of calcium on clinically relevant outcomes, it is widely accepted by cardiac anesthesiologists that these drugs might improve hemodynamics after CPB. The present results of the current survey further demonstrated that the majority of centers use 5 to 10 mg/kg or 10 to 15 mg/kg of calcium salts to facilitate CPB weaning.

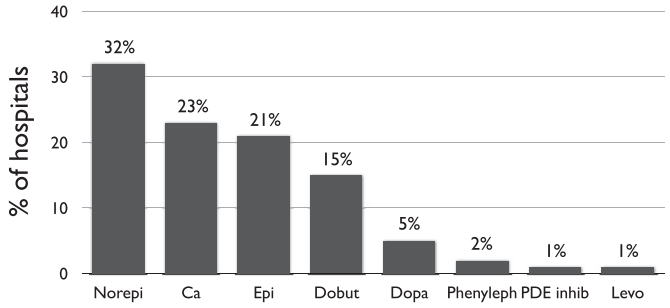

Fig 4. First-line drugs with inotropic and vasopressor properties used to support hemodynamics during termination of cardiopulmonary bypass.

Shapira et al. showed that the administration of 10 mg/kg bolus or 10 mg/kg bolus and a continuous infusion (1.5 mg/kg/min during 10 min) of calcium chloride immediately after CPB weaning caused a transient increase in cardiac index, stroke volume, and systolic and diastolic blood pressure.[8] Urban et al. also showed that administration of 10 mg/kg calcium chloride after termination of CPB caused a transient increase of cardiac output and of right ventricular ejection fraction.[9] On the other hand, other studies could not confirm the supposed beneficial hemodynamic effects of these drugs.[18,19]

Owing to the fact that calcium plays a key role in contraction of cardiomyocytes, it also is hypothesized that hypocalcemia, which often occurs during CPB, might be associated with difficult weaning from CPB. However, this inference holds only true for severe hypocalcemia, with ionized calcium levels of less than 0.75 mmol/L, which is rare in the majority of cardiac surgical patients.[10] Moreover, several studies conducted in critically ill patients did not find a significant association between hypocalcemia and mortality or other relevant clinical outcomes.[20,21] In cardiac surgery, an association between hypocalcemia and clinically relevant outcomes or mortality has never been studied. It should be noted that in cardiac surgical and critically ill patients, secretory response of parathyroid hormone to low calcium concentrations helps to normalize plasma level of this electrolyte.[22-24]

Calcium salts are not devoid of potential side effects, which include, but are not limited to, impaired response to beta-adrenomimetics, pancreatic injury, internal thoracic artery graft spasm, and the "stone heart" phenomenon.[10] An impaired response to beta-adrenomimetics was attributed to the use of calcium during CPB weaning.[25] Zaloga et al. demonstrated that a 10 mg/kg bolus of calcium chloride with a subsequent infusion of 2 mg/kg/h led to a blunted effect of epinephrine on blood pressure and on cardiac index.[25] Butterworth et al. also showed that an infusion of 1 mg/kg/min of calcium chloride over 20 minutes (approximately 1.600 mg for the average adult man) significantly inhibited the cardiotonic action of beta-adrenergic agonist epinephrine.[26] In contrast, in a randomized, blinded, placebo-controlled study Royster et al. studied the effect of low dose calcium chloride (5 mg/kg) administration on hemodynamics and on the response to an epinephrine infusion after emergence from CPB.[27] They found that calcium did not augment or inhibit the hemodynamic response to epinephrine.

Unfortunately, all aforementioned studies carry significant limitations. The majority of these studies were conducted more then 25 years ago, had a small sample-size, and were not powered to assess clinical relevant outcomes. Thus, considering the paucity of data indicating beneficial hemodynamic effects of calcium salts, in addition to other possible adverse effects, their effect during weaning from CPB remains uncertain. Accordingly, based on available evidence, the use of calcium salts to facilitate CPB weaning does not appear to be justified. Despite this, our survey showed that calcium is frequently administered by cardiac anesthesiologists all over the world during cardiac surgery, even when weaning from CPB is not difficult.

Pancreatic injury is a common finding in patients undergoing surgery under CPB and occurs in 69% of patients.[28] Postoperative pancreatic injury, defined as pancreatic hyperamylasemia, was observed in patients who receive more than 800 mg/m^2 (approximately 18 mg/kg for the average man) of calcium.

There is some evidence that calcium might impair internal mammary artery graft flow. Therefore, the influence of high-calcium dose (15 mg/kg) on internal mammary artery graft in patients after CABG could not be ignored,[29] although the quality of these findings is low.

One of the most serious complications of cardiac surgery is the development of the so-called "stone heart" phenomenon. This phenomenon, in part, might be attributed to so called "calcium paradox," when restoration of coronary blood flow after ischemic episode results in intracellular calcium overload, leading to myofibril hypercontraction, mitochondrial damage, and cell death. It is strongly believed that calcium administration may increase the risk of this phenomenon.[10] To avoid this complication, calcium salts should be given only after the end of reperfusion period and should be avoided in patients with suspected myocardial ischemia. Other systemic side effects that limit the use of calcium in the setting of cardiac surgery include undesirable tachycardia with consequent increase in myocardial oxygen consumption and decrease in potassium levels, leading to arrhythmias.

Of note, 12% (12 of 100) of the responders to this survey do not use calcium salts intraoperatively at all. Furthermore, there is no uniformity on the type of calcium salts that are used, calcium chloride versus calcium gluconate, or the duration of administration (bolus versus slow bolus). Although the majority of responders (58 of 88 66%) use calcium chloride for this purpose, in 19 out of 88 (22%) centers, calcium gluconate is used. Nonetheless, calcium gluconate appears not to be the ideal drug in these settings, as it is not metabolically active and requires hepatic metabolism to make the chelated calcium ions in its structure available.[10]

The authors acknowledge several limitations of the current survey. Despite a very high response rate of 89%, only 1 or 2 responses were obtained from the majority of countries. Thus, the results of the survey might have been affected by the sampling error. Completion of the survey by one representative from each department may not represent the routine practice of the department. In addition, the authors did not ask for reasons to refuse giving calcium intraoperatively (12% of responders). The authors did not collect the data on how calcium chloride or calcium gluconate were diluted before administration in different centers.

Conclusion

Overall, calcium salts seem to have both inotropic and vasoconstrictor properties and are therefore attractive for hemodynamic support during weaning from CPB. On the other hand, the risk of systemic side effects of calcium administration should be taken into consideration. The results of this survey demonstrated that calcium salts are widely used in adult patients to support hemodynamics during CPB weaning. However, there is no widely accepted practice regarding the type of

the drug, optimal dose, and mode of drug administration, especially during weaning from CPB. Unfortunately, no high quality evidence exists regarding safety and clinical efficacy of calcium salts in patients undergoing cardiac surgery. A large multicenter, randomized, double-blind, placebo-controlled trial (ICARUS trial) that is aimed to answer the question whether calcium chloride is beneficial during weaning from CPB is currently underway (NCT03772990). Given the results of the present survey, and the uncertainty about the beneficial effects of calcium salts, results of this trial will be of great interest for cardiac anesthesiologists.

Conflict of Interest

The authors acknowledge that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2020.02.010.

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