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Incidence of perioperative paediatric cardiac arrest before and after implementation of a specialised paediatric anaesthesia team.

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Abstract:	BACKGROUND: Perioperative critical events are still a major problem in paediatric anaesthesia care. Access to more experienced health-care teams might reduce the adverse event rate and improve outcomes. OBJECTIVE: This study analyses incidences of perioperative paediatric cardiac arrest (CA) before and after implementation of a specialised paediatric anaethesia team and training programme. DESIGN: Retrospective cohort study; before-and-after analysis. SETTING: Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Cologne, Germany. PATIENTS: 36,243 paediatric anaesthetics (0-18 yrs) between 2008 and 2016. INTERVENTION: Implementation of a specialised paediatric anaesthesia team and training programme in 2014, including (i) hands-on supervised training in all fields of paediatric anaesthesia, (ii) double staffing for critical paediatric cases, and (iii) an 24/7 emergency team. A logistic regression analysis with risk factors (age, ASA physical status grade [ASA-PS], emergency) was used to evaluate the impact of implementation of a specialised paediatric anaesthesia team. MAIN OUTCOME MEASURES: Incidences of perioperative paediatric CA and

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	anaesthesia-attributable CA before and after the intervention. RESULTS: Twelve out of 25 paediatric CAs were were classified as anaesthesia-attributable. The incidence of overall perioperative paediatric CA was 8.1/10,000 (95%-CI 5.2-12.7) in the period 2008-2013 and decreased to 4.6/10,000 (95%-CI 2.1-10.2) in 2014-2016. Likewise, the incidence of anaesthesia-attributable CA was lower after 2013 [1.6/10,000 (95%-CI 0.3-5.7) vs. 4.3/10,000 (95%-CI 2.3-7.9)]. In logistic regression, children anaesthetised after 2013 had nearly a 70 percent lower probability of anaesthesia-attributable CA (OR 0.306; 95%-CI 0.067-1.397; p=0.1263). For anaesthesia-attributable CA, young age was the most contributing risk factor whereas in overall paediatric CA, ASA-PS 3-5 played a more important role. CONCLUSION: In this study on incidences of perioperative paediatric CA from a European tertiary care university hospital, implementation of a specialised paediatric anaesthesia team and training programme was associated with lower incidences of perioperative paediatric CA and a reduced probability for anaesthesia-attributable CA.
Response to Reviewers:	Editor´s comments: Abstract: results; It is more logical to start with total incidence of CA and to show the incidence of anaesthesia-attributable CA thereafter. Response: - Thank you for this comment. This was modified in the revised manuscript. (p2 l39) -Introduction, last para: We hereafter analyse the incidences and causes of perioperative paediatric CA, especially those attributable to anaesthesia, in a German tertiary care university hospital before and after implementing a special paediatric anaesthesia team and training programme in 2014. Response: - The proposed wording has been incorporated into the revised manuscript. (p4 l39 ff) - Methods: p5, L4-8: according to what is described in the Setting section, I suggest the following: Study design: A machine-readable anaesthesia record was implemented in our department in 2008 to allow the electronical storage of our data. In addition, it is mandatory in our institution to report any perioperative complication on a specific critical incident report form. This report is written by the anaesthesia team involved in the case and stored together with the anaesthesia record in a dedicated database. We screened all critical incidents reports and reports on perioperative CA within 24h postoperatively in patients younger than 18 years collected between Feb 2008 and Dec 2016. A cardiac arrest (CA) was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation requiring cardiopulmonary resuscitation. Critical incidents from the intensive care unit were excluded from this analysis to focus on anaesthesia associated problems. The patient's anaesthesia and medical recorts, and the critical incident report form on each cardiac arrest were analysed independently by three investigators (A.H., U.T., S.A.P.). Setting: Our department provides paediatric anaesthesia for …. Statistics: Rates of CA are shown as incidences per 10,000 anaesthetics and 95% confidence (95%-CI) intervals. Response: Thank you for these suggestions. The text has been modified and restructured accordingly. -p6, L9: As a result the majority of paediatric cases was managed by the rest of the team with varying staff and a fluctuating paediatric anaesthetic experience. Thus, there was limited training in paediatric anaesthesia in some areas of our department. Response: -The proposed wording has been incorporated into the revised manuscript. (p5 l52) -p7, L49: Content Response: -Please excuse this mistake. This was corrected in the revised manuscript. (p7 l29) -p8, L11: regional anaesthesia related instead of block? Response: -This was modified in the revised manuscript (p7 l56) and Fig. 3. - p9, L23-9: It is more logical to start with total incidence of CA and to show the

incidence of anaesthesia-attributable CA thereafter.
Response:
-This was modified in the abstract and results sections (p9 l23)

- p9, L29: when looking to table 1 and fig 1, one realizes that what happened in 2015 is contradictory with your thesis: increase in both total CA rate and proportion of anaesthesia attributable ones. This deserves an explanation. One could argue that the decrease in CA occurred only by chance in 2014 and 2016….
Response:
-Thank you for this comment. We agree that the reduction in anaesthesia-attributable CA in 2014-2016 compared with previous years was not statistically significant (p=0.13) and we can therefore not claim to demonstrate an effect with certainty. The frequencies of any CA and anaesthesia-attributable CA respectively was in 2015 the same as in 2009 and 2013, although the calculated incidences decreased slightly. However, one should note that the total number of paediatric anaesthesias was 10% higher in the period 2014-2016, and even nearly 20% higher in children ≤3 years. This is more clearly stressed in the revised manuscript (p11 l19 ff). However, overall, we could demonstrate that in the logistic regression, children anaesthetised after 2013 had nearly a 70 percent lower probability of anaesthesia-attributable CA at our institution during the study period.

-p9,L39: the fact that emergency did not appear to be a risk factor is probably only the result of having a paediatric emergency team available for every case. Please comment.
Response:
-The emergency team was implemented in 2014 but emergency was found not to be a risk factor for the whole study period. Since only 17% of cases were emergencies (non-elective cases), the numbers of such cases were too small to analyse either the role of emergency status on the risk of CA or the effect of implementation of the specialised team on the risk for emergency cases alone. This is discussed now in the revised manuscript (p11 l41 ff).

-p9,L59: Eight CAs were completely related to anaesthesia, in four CAs, anaesthesia at least was contributory. It would be most interesting to add the data of supplemental data 2 as a table in the text. This would make the interpretation of the last part of the results easier.
Response:
-We fully agree that it would be helpful for the reader to have patient details in the text. We originally moved it into the digital supplement for space reasons. The revised manuscript now contains the patient details (Table 3).

-p11: Discussion: In this retrospective cohort study, the incidence of both overall perioperative CA and anaesthesia attributable CA was on average lower after implementation of a specialised paediatric anaesthesia team and a training programme despite of an increase in the proportion of children aged…. Your data proof that having a specialized team available for every paediatric case decreased the incidence of CA at least in 2014 and 16. It would be nice if you could also prove that t decreased morbidity: e.g. incidence of laryngospasm. The training programme was certainly useful but how can you prove it? Establishing written SOPs was probably also a major change…
Response:
-The wording (on average) in the first sentence of the discussion section was modified.
-Our study focused on perioperative CA as an established endpoint and quality marker. We fully agree that CA is not a perfect endpoint, especially in paediatric anaesthesia. Unfortunately, with our database we were not able to analyse other relevant morbidity factors (eg. laryngospasm). This limitation is already addressed in the manuscript (p12 l60 ff): "However, while CA is a rare perioperative event, studies also need to analyse other complications in paediatric anaesthesia (eg, respiratory problems, medication errors, etc.)."
-Establishing SOPs was of course an important change in our department and may have contributed to a better quality in paediatric anaesthesia. Since all measures were implemented as a bundle we cannot evaluate specific effects of different parts of the intervention. Moreover, as our study is retrospective, we cannot prove causality. These limitations were already addressed in the manuscript (p13 l17 ff). However, most

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studies in this area are naturally retrospective.

- p11, L15: and the high incidence of CA observed in 2015!
Response:
-see comment above. the seemingly high incidence of CA in 2015 is more clearly addressed in the revised manuscript (p11 l19 ff).

Reviewer Comments:
Reviewer #1:
The authors have satisfactorily addressed all comments by this reviewer.
The mansucript would benefit from substantial English language revision and shortening when doing so.
Response:
-Thank you for this comment and your assessment. The manuscript has been revised linguistically by a native speaker.

Reviewer #2:
I would like to thank the authors for answering the reviewers' comments.
Only minor changes were made in the manuscript, and the major limitations remain (e.g. small incidence of primary endopint and several confounding factors could be missing).

1. What is the predictive accuracy of the multivariable logistic model (C-Stat or AUROC)?
Response:
All CA, step function for year: AUROC = 0.919; Attributable CA, step function for year: AUROC = 0.916. (see p8 l19)

2. Table 2: How can only one p value be given for the age groups? I would suggest ref < 1, 1-3, >3.
Response:
The p-value is for the overall effect of age, i.e., differences between all three groups <1, 1-3 and >3 years. P-values were calculated using Wald chi-square tests of the joint effect of the parameters for each categorical variable in the model.

Bottom line, hard to formulate any strong recommendations based on that small study.
No guarantee that the model applied at the authors' center is the best either.
Response:
-Of course, the number of paediatric perioperative CA is (mercifully) low, but the observation period is long (9 years) and the population is large (>30,000 paediatric anaesthesias). Thus, our study is one of the largest European studies on this topic. Implementation of a specialised team and training programme was associated with a reduced incidence of CA at our institution. Due to the retrospective study design we cannot comment on causality, and as it is a single center study, our results are not generalisable and probably this approach does not work in other hospitals. Both these limitations were already discussed in the original manuscript (p13 l17 and p13 l58). However, we feel that a specialisation and an adequate individual case load in paediatric anaesthesia are important factors to improve safety and quality.

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Incidence of perioperative paediatric cardiac arrest before and after implementation of a specialised paediatric anaesthesia team.

Running head: Incidence of perioperative paediatric cardiac arrest.

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Abstract:

BACKGROUND: Perioperative critical events are still a major problem in paediatric anaesthesia care. Access to more experienced health-care teams might reduce the adverse event rate and improve outcomes.

OBJECTIVE: This study analyses incidences of perioperative paediatric cardiac arrest (CA) before and after implementation of a specialised paediatric anaethesia team and training programme.

DESIGN: Retrospective cohort study; before-and-after analysis.

SETTING: Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Cologne, Germany.

PATIENTS: 36,243 paediatric anaesthetics (0-18 yrs) between 2008 and 2016.

INTERVENTION: Implementation of a specialised paediatric anaesthesia team and training programme in 2014, including (i) hands-on supervised training in all fields of paediatric anaesthesia, (ii) double staffing for critical paediatric cases, and (iii) an 24/7 emergency team. A logistic regression analysis with risk factors (age, ASA physical status grade [ASA-PS], emergency) was used to evaluate the impact of implementation of a specialised paediatric anaesthesia team.

MAIN OUTCOME MEASURES: Incidences of perioperative paediatric CA and anaesthesia-attributable CA before and after the intervention.

RESULTS: Twelve out of 25 paediatric CAs were were classified as anaesthesia-attributable. The incidence of overall perioperative paediatric CA was 8.1/10,000 (95%-CI 5.2-12.7) in the period 2008-2013 and decreased to 4.6/10,000 (95%-CI 2.1-10.2) in 2014-2016**.** Likewise, the incidence of anaesthesia-attributable CA was lower after 2013 [1.6/10,000 (95%-CI 0.3-5.7) vs. 4.3/10,000 (95%-CI 2.3-7.9)].

In logistic regression, children anaesthetised after 2013 had nearly a 70 percent lower probability of anaesthesia-attributable CA (OR 0.306; 95%-CI 0.067-1.397; p=0.1263). For anaesthesia-attributable CA, young age was the most contributing risk factor whereas in overall paediatric CA, ASA-PS 3-5 played a more important role.

CONCLUSION: In this study on incidences of perioperative paediatric CA from a European tertiary care university hospital, implementation of a specialised paediatric anaesthesia team and training programme was associated with lower incidences of perioperative paediatric CA and a reduced probability for anaesthesia-attributable CA.

Keywords:

Cardiac arrest, complications, anaesthesia

Introduction:

Perioperative cardiac arrest (CA) is a dramatic and serious complication but was previously described as the stepchild of emergency medicine.[1] However, current resuscitation guidelines now include a section on perioperative cardiac arrest [2], underlining the relevance of this special situation.

In recent literature, it is well documented that children have a higher incidence of perioperative CA than adults [3, 4], and in a study from our institution, 5 out 12 anaesthesia-related CAs in an unselected (adult and paediatric) cohort of 169,500 anaesthetics occurred in paediatric patients.[5] Studies on perioperative paediatric CA [6-15] were predominantly conducted at specific pediatric hospitals.[7, 10, 13-15]

A recent pan-European multicentre study revealed a high rate of severe critical events in a large perioperative paediatric cohort, with a relevant impact of the anaesthesiologist´s experience on the rate of complications, especially in critically ill and young children. Furthermore, this important study found a variable incidence across Europe [16] and moreover, the risk for cardiovascular critical events in patients ASA-PS III-V was higher for occasional or frequent providers compared to dedicated providers of paediatric anaesthesia. Another ongoing European research project (NECTARINE) focuses on anaesthesia practice and outcomes in neonates and young infants, underlining that this group is at high risk for perioperative complications.[17] Access to more experienced health-care teams might reduce the adverse event rate and improve outcomes.[16, 18]

In this report, we analyse the incidences and causes of perioperative paediatric CA, especially those attributable to anaesthesia, in a German tertiary care university hospital before and after implementing a special paediatric anaesthesia team and training programme in 2014.

~~Thus, in our study, we analyse incidences of perioperative paediatric CA in a German tertiary care university hospital between 2008 and 2016. Furthermore, we assess incidences of perioperative paediatric cardiac arrest and anaesthesia-attributable CA before and after implementation of a special paediatric anaesthesia team and training programme.~~

Methods

Ethics approval

Ethics approval was waived by the local Ethics Committee of the University Hospital of Cologne due to the retrospective nature of the study (Ethics Committee N° 17-396).

Study design

A machine-readable anaesthesia record was implemented in our department in 2008 to allow the electronic storage of our data. In addition, it is mandatory in our institution to report any perioperative complication on a specific critical incident report form. This report is written by the anaesthesia team involved in the case and stored together with the anaesthesia record in a dedicated database. We screened all critical incidents reports and reports on perioperative CA within 24h postoperatively in patients younger than 18 years collected between Feb 2008 and Dec 2016. A cardiac arrest (CA) was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation requiring cardiopulmonary resuscitation.[19, 20] Critical incidents from the intensive care unit were excluded from this analysis to focus on anaesthesia associated problems. The patient's anaesthesia protocol, medical records, and the critical incident report on each cardiac arrest were analysed independently by three investigators (A.H., U.T., S.A.P.).

Setting

Our department provides paediatric anaesthesia for many different surgical specialities: classical paediatric surgery, neurosurgery, cardiac surgery, orthopaedics, ENT, ophthalmic surgery, urology, maxillo-facial surgery and dental medicine, cardiac catheterisation, radiologic imaging (e.g. MRI) and other diagnostic procedures. Before 2014, only a small group (5-6) of anaesthetists dealt predominantly (50-80%) with paediatric anaesthesia, mainly in diagnostic procedures and cardiac surgery as well as cardiac catheterisation, and only occasionally in other departments. Overall, they were able to cover only about 25% of the paediatric cases in the hospital. As a result, the majority of paediatric cases was managed by the rest of the team with varying staff and a fluctuating paediatric anaesthetic experience. ~~Thus, there was limited training in paediatric anaesthesia in some areas of our department.~~

Intervention

In 2014, a specialised paediatric anaesthesia team and training programme was implemented at our institution, and nowadays about 80-90% of all paediatric cases can be covered by the specialised team. Beside daily practice in the field of 'classical' paediatric anaesthesia, the training programme included practice in paediatric cardiac intensive care, in anaesthesia and sedation for cardiac catheterisation and other interventional or diagnostic procedures.

The training team consists of two anaesthetists (consultants) and a specially trained nurse. One of the anaesthetists is from the 'experienced group' with 2 to >15 years of practice in paediatric anaesthesia and paediatric intensive care and one from the 'training group' (0.5 and 2 years of specialised paediatric anaesthesia training). Furthermore, a monthly teaching session for paediatric anaesthesia was introduced and supervision of sedation for diagnostic procedures was improved. The composition and training of our specialised team was built on the basis of the 'European guidelines for training in paediatric anaesthesia', which were published in 2007 by the Federation of European Association of Paediatric Anaesthesia (FEAPA), the predecessor of the European Society of Paediatric Anaesthesia (ESPA), and which are still an excellent basis for training.[21]

As part of these measures, the specialised anaesthesia team increased to nearly 20 members and since then well-trained paediatric anaesthetists are available even in remote operation areas for both routine paediatric cases and children at high risk (eg. congenital heart disease). For very young children and in children at high risk there are always two experienced anaesthetists to take care of the patient.

The introduction of the specialised paediatric anaesthesia team was combined with further measures:

- Before 2014 standard operating procedures (SOP) were present only for paediatric cardiac surgery. In 2014, a broad spectrum of most aspects of paediatric anaesthesia was added, including premedication, monitoring, vascular access, fluid management, regional anaesthesia, cardiovascular management of preterm infants, prevention of postoperative nausea and vomiting, pain therapy and a revised dosage list.
- A monthly teaching session for paediatric anaesthesia was introduced, and a separate monthly teaching for nurses as well.

- Yearly EPLS-courses according to the European Guideline of the European Resuscitation Council were started already in 2012 with 4-5 participants from our own department; in 2014 about 10 anaesthetists had completed this training in paediatric resuscitation.
- Moreover, an emergency team (two anaesthetists and a specially trained nurse) is available 24/7 to improve anaesthetic care in paediatric emergencies.
- During day time, the specialised paediatric team can also be made available for anaesthesia in cases in which problems occur or are foreseen and where paediatric anaesthetists are not regularly present.

In summary, in 2014 (i) a hands-on supervised training in all fields of paediatric anaesthesia, (ii) double staffing for critical paediatric cases (<2 yrs, ASA>2, and every time the responsible team requested support from a special paediatric anaesthetist), and (iii) a 24/7 emergency team was implemented at our institution.

Anaesthesia-attributable cardiac arrest

A classification modified from the Australian system of classification by State-Based Anaesthesia Mortality Committees was used to categorise CA **(Supplemental Digital Content 1).**[22]

- Anaesthesia-related CA was defined as cardiac arrest that is caused directly by anaesthetic measures in context of surgery or interventional procedures (*Category 1*).
- Anaesthesia-contributory CA was defined as cardiac arrest caused by both surgical and anaesthesia associated factors or where there is some doubt whether CA was entirely attributable to the anaesthesia or other factors under the control of the anaesthetist (*Category 2-3*).
- Anaesthesia-attributable CA was defined as CA according to category 1 (anaesthesia-related CA) or category 2 (anaesthesia-contributory CA).

Adverse events leading to cardiac arrest

Following this, the primary adverse events leading to CA were further graded similar to the categories used by Cheney *et al*.: 1) respiratory, 2) cardiovascular, 3) medication-related, 4) equipment-related, 5) ~~block~~ regional anaesthesia-related, 6) procedural, 7) iatrogenic, and 8) other not further classified incidents.[23]

Finally, CAs were classified by the reviewers as 1) definitely preventable, 2) possibly preventable, or 3) not preventable.

Statistics

Rates of CA are shown as incidences per 10,000 anaesthetics and 95% confidence (95%-CI) intervals. Logistic regression analysis with a step-function (before and after 1 Jan 2014) was used to identify risk factors which are independently associated with the endpoint (CA). In addition to year, ASA-PS, age and emergency indication were included as categorical covariates, with backward stepwise selection. A $p<0.05$ level of significance was chosen. Results of logistic regression analysis are reported as odds ratios (OR) with 95% confidence intervals (95%-CI); overall predictive accuracy was assessed using the area under the ROC curve. Risk factor analysis was carried out by comparing the incidence of cardiac arrest between the particular groups. Categorical variables were calculated as numbers and percent. Data were documented with Microsoft Excel 2013® (Microsoft, Redmond, WA, USA) and analysed with SAS® software version 9.3 (SAS Institute Inc., Cary, NC, USA)

Results

During the study period, 36,243 paediatric anaesthetics (0-18 yrs) were performed. The number and proportion of anaesthetics in children younger than 3 years and the rate of patients classified as ASA-PS 3-5 increased steadily during the observation period **(Table 1)**. Likewise, the proportions of children < 1 yr and < 1yr + ASA-PS 3-5 were greater in the population 2014-2016 compared to 2008-2013.

Between Feb 2008 and Dec 2016, we identified 25 reports on perioperative paediatric CA. This is in an overall incidence of 6.9 perioperative CAs (95%-CI 4.7-10.2) per 10,000 anaesthetics. The overall incidence (n=12) of anaesthesia-attributable CA was 3.3/10,000 (95%-CI 1.9-5.8) anaesthetics between 2008 and 2016 **(Table 1)**. During the study period, the annual incidences of CA varied from 2.5 to 12.2 per 10,000 anaesthetics, and from 0.0 to 9.1 per 10,000 anaesthetics for anaesthesia-attributable CA.

The incidence of overall perioperative paediatric CA was 8.1/10,000 (95%-CI 5.2-12.7) in the period 2008-2013 and decreased to 4.6/10,000 (95%-CI 2.1-10.2) in 2014-2016 **(Figure 1, Table 1)**. Likewise, the incidence of anaesthesia-attributable CA was lower after 2013 [1.6/10,000 (95%-CI 0.3-5.7) vs. 4.3/10,000 (95%-CI 2.3-7.9)].

Logistic regression analysis with risk factors age, ASA-PS, and emergency, revealed younger ages and ASA-PS 3-5 as significant risk factors for perioperative CA in general and anaesthesia-attributable CA. As the inclusion of a not significant factor increases the influence of random scattering on the results of the regression, the non-significant factor “emergency” was removed from the further statistical analysis. **Table 2** shows the odds ratios for CA in different subgroups. Infants and children at younger ages had a statistically significantly higher risk for perioperative CA in general, and in particular for anaesthesia-attributable CA. The odds ratio for ASA-PS 3-5 compared to ASA-PS 1-2 was greater for any perioperative CA than for anaesthesia-attributable CA. Children anaesthetised between 2014-2016 were at lower risk (OR 0.306; 95%-CI 0.067-1.397; p=0.1263) for anaesthesia-attributable CA. However, this effect was not statistically significant.

Eight CAs were related to anaesthesia alone, in four CAs, anaesthesia was contributory, and 13 CAs were classified unrelated to anaesthesia. From 25 patients with CA, 23 were classified ASA PS 3-5. Sixty percent (15/25) of CAs occurred in children aged younger than 1 year. Cardiac arrest was assessed as definitely preventable in two cases **(Table 3)**. In both cases, an accidental medication error led to CA, and both preventable incidents occurred during the first period (2008-2013).

In 11 out of 12 (91.7%) anaesthesia-attributable CAs, patients were aged 3 years or younger. Fifty percent (n=6) of children with anaesthesia-attributable CA were aged younger than 1 year. Seven patients did not survive perioperative CA to hospital discharge. In three cases, severe trauma led to CA and in three other cases fatal CA occurred during heart catheterisation.

Fourteen (56%) CAs occurred during cardiac surgery or heart catheterisation. **Figure 2** shows the number of perioperative paediatric CAs in children undergoing cardiac procedures (cardiac surgery or cardiac catheterisation). The proportion of anaesthesia-attributable CA was higher in the non-cardiac setting compared to cardiac procedures. In the period 2014-2016, no CA occurred in the non-cardiac setting.

In 6 out of 12 anaesthesia-attributable CAs, respiratory and airway problems were the primary adverse events leading to CA whereas in all CAs cardiovascular problems were the leading adverse events (15/25) **(Figure 3).**

Discussion

Main findings

In this retrospective cohort study, the incidence of both overall perioperative CA and anaesthesia attributable CA was on average lower after implementation of a specialised paediatric anaesthesia team and a training programme despite of an increase in the proportion of children aged <1 year and an increase in the proportion of patients aged younger than 1 year and classified as ASA-PS 3-5. Although children anaesthetised after 2013 had nearly a 70 percent lower probability of anaesthesia-attributable CA, this effect was not statistically significant. The low frequencies of CA during the study period may explain the lack of statistical significance. A longer second observation period would possibly have increased the chance to find a significant reduction of CA. Moreover, the number of anaesthesia-attributable CAs could not be reduced to zero by our measures. However, the seemingly high number of anaesthesia-attributable CAs in 2015 should be interpreted with caution as the total number of anaesthetics in children aged 3 years and younger was about 20% higher in the period 2014-2016.

Young age was the most strongly contributing risk factor to anaesthesia-attributable CA whereas in overall paediatric CA, ASA-PS 3-5 played a more important role. However, confidence intervals for odds ratios were wide. Age and ASA-PS have previously been described as potential risk factors of perioperative paediatric CA.[7-11, 13, 15] Interestingly, emergency status appeared not to be a significant risk factor of CA in our study population, and we could not demonstrate a difference in incidences of CA in emergencies before and after the intervention. Probably, the number of such cases were too small to analyse either the role of emergency status on the risk of CA or the effect of implementation of the specialised team on the risk for emergency cases alone. However, most of the studies report that children undergoing emergency procedures are at a higher risk for perioperative CA.[6, 7, 9, 11, 24, 25] but, in a recent study there was also no difference in perioperative paediatric CA between elective and non-elective cases.[13]

During the study, 91.7% (11/12) of anesthesia-related CA occurred in children ≤ 3 years, indicating that this group has a high risk for perioperative complications.[26]

In our study, the number of CAs was higher in children undergoing cardiac procedures. These findings are in agreement with several studies on perioperative complications in children.[8, 10, 13, 16] The proportion of anaesthesia-attributable CA was greater in the children undergoing non-cardiac procedures. By expanding a special team, well-trained pediatric anesthesiologists were increasingly available for all other surgical areas, and notably, after implementation of a specialised paediatric anaesthesia team, no more CAs occurred in the non-cardiac setting. However, the continued occurrence of CA in cardiac procedures after 2013 show that cardiac intervention is still a risk area in our hospital. Unfortunately, we cannot provide the exact individual case-load of the specialised paediatric anaesthesia group. However, as paediatric anaesthetists were more often available for paediatric cases in all surgical areas of our hospital since 2014, we expect that the individual case-load remained constant or even increased despite an increasing number of physicians in the paediatric group. From the literature, a minimum of 200 paediatric cases annually [27], or 50 cases annually in children < 3 years [28] are recommended to acquire sufficient competence. Recent studies showed that longer years of experience and a high individual case-load in paediatric anaesthesia have beneficial effects on complication rates and incidences of CA.[13, 26]

Respiratory and airway problems accounted for most anaesthesia-attributable CAs followed by cardiovascular events. Respiratory or cardiovascular events were major causes in most of the studies in perioperative paediatric CA.[6-11, 13] Both preventable CAs due to medication errors occurred in the first period (2008-2013). This might be a further indicator that management of anaesthesiological paediatric care improved after implementation of a specialised training and team.

The findings of our present analysis and the results of recent studies stress the importance of educational measures and overall quality improvement in paediatric anaesthesia.[16, 29, 30]

Seven children did not survive CA to hospital discharge. All non-survivors were in the group with CA unrelated to anaesthesia, suggesting that the chance to survive anaesthesia-attributable CA might be higher than for CA unrelated to anaesthesia.

As data on survival to hospital discharge was derived from the hospital information system, we cannot comment on neurological outcome.

Strengths

The strengths of our study are a large study population and a clear and important clinical endpoint (CA). Cardiac arrest is an established endpoint used in many studies and can serve as a quality indicator.[5, 6, 8, 9, 11, 13, 24, 31, 32] However, CA is a rare perioperative event and studies also need to analyse other complications in paediatric anaesthesia (eg, respiratory problems, medication errors, etc.). Furthermore, a standardised scoring system [22] was used which enables direct comparison with some other studies in the field of perioperative complications.[5, 15, 33] Our data from a tertiary care university hospital represent a broad anaesthesiological spectrum and a typical hospital paediatric patient mix including cardiac procedures. Thus, our results might be representative for teaching hospitals with a variably experienced staff in paediatric anaesthesia.

Limitations

The present study has some important limitations. As it is a retrospective and observational analysis, we are not able to comment on causality or to evaluate specific effects of different parts of the intervention. Furthermore, we cannot define an exact point in time from which our measures took an effect. Even though our anesthesia protocol is machine-readable, only a few fields (i.e. ASA, age, emergency) were reliably filled out. Therefore, we had to limit ourselves to these parameters for the analysis, and we cannot comment on the effect of other variables like surgical complexity or comorbidities. Furthermore, we cannot exclude that other factors may have changed during the study period and contributed to the reduction of incidences of CA, especially as frequencies of CA appeared to be lower in the period 2011-2013 compared to 2008-2010.

Moreover, as we depend on reporting by our staff anaesthesiologists, it is possible that some critical incidents were missed. We chose a time period of 24 hours postoperatively and thus, probably not all postoperative complications in outpatients were captured. Therefore, we might have missed some incidents in the late perioperative period. However, our analysis focuses on anaesthesia-attributable CA and most anaesthesia-related complications are likely to appear in the intraoperative or early postoperative period. Furthermore, critical incident reports were reviewed by institutional members. Therefore, it is possible that not all incidents were classified correctly as attributable or unrelated to anaesthesia. The differences in study design, observation periods, and definitions of perioperative complications, or outcomes limit the comparability of the different studies in this field. So far, there is no consensus on documenting complications and defining anaesthesia-related mortality.[34] Finally, as a single-centre study our results may not be generalisable.

Conclusions

Children are at increased risk of perioperative CA. Young age, ASA physical status grade and cardiac procedures contribute as risk factors. Specialised paediatric anaesthesia staff and implementation of paediatric anaesthesia training guidelines are mandatory to handle high risk procedures and may be an important factor for further paediatric perioperative CA risk reduction.

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Cologne, 17 May 2018

Dear Professor Veyckemans,

please find enclosed a revised version of our manuscript (EJA-D-18-00090R2) for consideration for publication in the European Journal of Anaesthesiology.

We thank you and the reviewers for the time and efforts reviewing our manuscript. We revised the manuscript according to the comments and suggestions. Along with the revised manuscript we submit a point-by-point response to the respective questions raised. We hope that the helpful comments have led to a major improvement of our manuscript and the manuscript is of potential interest to the readers of the EJA and suitable for publication in your journal.

On behalf of all authors,
Yours sincerely

A. H

Andreas Hohn

Table 1

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2008-2016
paediatric anaesthetics (n)	3282	3804	3997	4170	4170	3978	4038	4413	4391	36243
age < 1 yr (n)	461	519	561	578	569	532	620	737	769	5346
age 1-3 yrs (n)	474	641	674	710	629	661	658	661	763	5871
age > 3 yrs (n)	2347	2644	2762	2882	2972	2785	2760	3015	2859	25026
ASA-PS 3-5 (%)	21.6	22.2	19.9	19.2	17.6	21.3	22.3	23.5	27.6	195.2
age < 1 yr (%)	14.0	13.6	14.0	13.9	13.6	13.4	15.4	16.7	17.5	14.8
age ≤ 3 yrs (%)	28.5	30.5	30.9	30.9	28.7	29.9	31.6	31.7	34.9	30.9
non-elective procedures (%)	17.5	18.2	16.9	19.9	16.5	16.9	16	16.2	16.7	17.2
cardiac arrest (CA) (n)	4	3	2	3	4	3	1	3	2	25
anaesthesia-attributable cardiac arrest (n)	3	2	2	0	1	2	0	2	0	12
incidences (95%-CI) of overall CA/10,000 anaesthetics	12.2 (4.7-31.3)	7.9 (2.1-23.2)	5.0 (0.9-18.2)	7.2 (2.0-21.1)	9.6 (3.7-24.6)	7.5 (2.1-22.2)	2.5 (0.1-14.0)	6.8 (1.9-20.0)	4.6 (0.8-16.6)	
incidences (95%-CI) of anaesthesia-attributable CA/10,000 anaesthetics	9.1 (2.5-26.8)	5.3 (0.9-19.2)	5.0 (0.9-18.2)	0.0 (0.0-9.2)	2.4 (0.1-13.6)	5.0 (0.9-18.3)	0.0 (0.0-9.5)	4.5 (0.8-16.5)	0.0 (0.0-8.7)	
incidences (95%-CI) of overall CA/10,000 anaesthetics	8.1 (5.2-12.7)						4.6 (2.1-10.2)			6.9 (4.7-10.2)
incidences (95%-CI) of anaesthesia-attributable CA/10,000 anaesthetics	4.3 (2.3-7.9)						1.6 (0.3-5.7)			3.3 (1.9-5.8)

Table 1 Annual numbers of paediatric anaesthetics and rates of patients classified ASA-PS 3-5, age distributions, rates of non-elective procedures.

Annual numbers and incidences (95%-CI) of overall perioperative paediatric cardiac arrest (CA) and anaesthesia-attributable CA of each year.

Table 2

any cardiac arrest				
odds ratio estimates				
effect	point estimate	95% Wald confidence limits		p-value
age <1 year vs >3 years	6.569	2.142	20.146	0.0039
age 1-3 years vs >3 years	5.389	1.517	19.140	
ASA-PS 3-5 vs ASA-PS 1-2	27.159	6.207	118.843	<.0001
year 2014-2016 vs 2008-2013	0.477	0.190	1.195	0.1142
anaesthesia-attributable cardiac arrest				
odds ratio estimates				
effect	point estimate	95% Wald confidence limits		p-value
age <1 year vs >3 years	14.482	1.719	122.025	0.0386
age 1-3 years vs >3 years	14.991	1.673	134.364	
ASA-PS 3-5 vs ASA-PS 1-2	11.246	2.320	54.522	0.0027
year 2014-2016 vs 2008-2013	0.306	0.067	1.397	0.1263

Table 2 Results of the logistic regression analysis with risk factors age, ASA-PS, and emergency*. Odds ratios of cardiac arrest (any) and anaesthesia-attributable cardiac arrest in different subgroups.

*emergency was removed from the analysis as there was no significant effect in any group.

Table 3

no.	age	sex (m/f)	ASA PS	speciality	emergency	adverse event leading to CA	category	outcome	anaesthesia technique	preventability	category
1	2 wks	f	4	cardiac surgery	yes	aorto-pulmonary artery shunt for tetralogy of Fallot; dislocation of the endotracheal tube leading to hypoxia and CPR	respiratory	recovered	GA	possible	anaesthesia-related
2	1 mth	m	3	cardiology/ heart catheterisation	no	hypoplastic left heart syndrome with aortic stenosis; CA during airway manipulation due to airway leakage	respiratory	recovered	GA	possible	
3	4 mths	m	2	ophthalmologic surgery	no	former preterm (24 wks); accidental bolus of remifentanil; apnoe and bradycardia	medication-related	recovered	GA	definite	
4	9 mths	m	3	endoscopic intervention	no	percutaneous enteral gastrostomy (PEG); difficult airway and laryngospasm; short CPR during bradycardia	respiratory	recovered	GA	no	
5	6 mths	f	4	ENT surgery	no	stridor due to epidermolysis bullosa; diagnostic intervention (bronchoscopy); CVCI after induction	respiratory	recovered	GA	no	
6	1 yr	m	3	vascular surgery	yes	former preterm (33 wks); dislocated Broviac catheter; difficult mask ventilation due to macroglossia; failed endotracheal intubation; hypoxic CA	respiratory	recovered	GA	possible	
7	2 yrs	f	2	oncology, diagnostic	no	diagnostic intervention (bone-marrow puncture); ventilation via face mask failed; hypoxic CA	respiratory	recovered	GA	no	
8	8 yrs	m	3	vascular surgery	yes	removal of an infected Demers atrial catheter; vasovagal asystole during induction	cardiovascular	recovered	GA	no	
9	3 wks	m	4	abdominal surgery	yes	acute preload reduction due to rapid ascites drain after Tenckhoff tunneled peritoneal catheter placement	cardiovascular	recovered	GA	possible	anaesthesia-contributory
10	2 yrs	m	3	cardiology/ heart catheterisation	no	hypoplastic left heart syndrome; bradycardia and hypoxia after extubation	cardiovascular	recovered	GA	possible	
11	2 yrs	m	4	neurosurgery	no	asystole during CVC placement; short period of CPR	cardiovascular	recovered	GA	no	
12	3 yrs	m	4	cardiology/ heart catheterisation	no	asystole and CPR during transfer after catheter septal ablation for HOCM	cardiovascular	recovered	GA	no	
13	1 mth	f	4	cardiology/ heart catheterisation	yes	pulmonal atresia, ventricular septal defect, triscuspidal regurgitation; CPR during a pulmonary hypertensive crisis a week ago; CPR during catheter intervention	cardiovascular	death	GA	no	unrelated to anaesthesia
14	3 mths	f	3	cardiology/ heart catheterisation	no	aortic stenosis after Norwood procedure; asystole during guide wire manipulation	cardiovascular	recovered	GA	no	
15	3 mths	f	3	cardiology/ heart catheterisation	no	aortic stenosis after Norwood procedure; complete atrioventricular block requiring CPR	cardiovascular	recovered	GA	no	
16	4 mths	f	4	cardiology/ heart catheterisation	yes	cardiac failure after Norwood procedure; CPR during catheter intervention	cardiovascular	recovered	GA	no	
17	6 mths	f	4	cardiology/ heart catheterisation	y	tetralogy of Fallot;	cardiovascular	death	GA	no	

						pulseless electrical activity due to guide wire manipulation; CPR and ECLS					
18	5 mths	f	3	ophthalmological surgery	no	adult dose of eye drops causing bradycardia	medication-related	recovered	GA	definite	
19	2 yrs	m	5	cardiac surgery	yes	displaced aortic cannula	equipment-related	recovered	GA	possible	
20	1 d	m	5	cardiology/ heart catheterisation	yes	hypoplastic left heart syndrome; CPR during catheter intervention	cardiovascular	death	GA	no	
21	3 d	f	4	neurosurgery	no	choroid plexus papilloma; haemorrhage and CA during craniotomy	cardiovascular	recovered	GA	no	
22	3 wks	m	4	cardiology/ heart catheterisation	no	total anomalous pulmonary venous connection (TAPVC); CPR during catheter intervention	cardiovascular	death	GA	no	
23	8 yrs	m	5	cardiac surgery	yes	drowning accident, emergency cardiopulmonary bypass; CPR	cardiovascular	death	GA	no	
24	14 yrs	m	5	neurosurgery	yes	severe traumatic brain injury	not further classified	death	GA	no	
25	15 yrs	m	5	cardiac surgery	yes	penetrating thoracic injury	cardiovascular	death	GA	no	

Table 3 Details of patients with perioperative CAs between 2008 and 2016.

CA, cardiac arrest
CVC, central venous catheter
CVCI, cannot ventilate – cannot intubate
CPR, cardiopulmonary resuscitation
ECLS, extracorporal life support
GA, general anaesthesia
HOCM, hyprtrophic obstructive cardiomyopathy

Figure 1

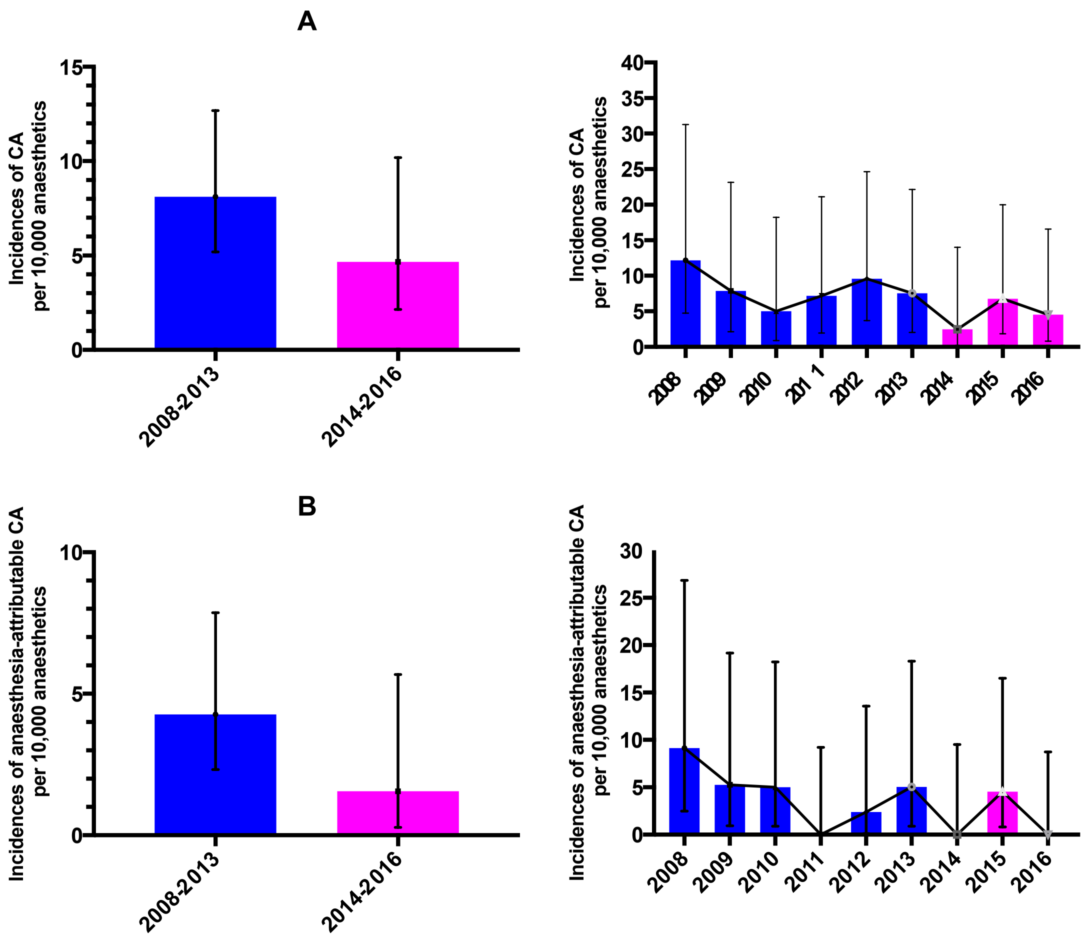

Figure 1 Incidences of **A)** overall perioperative cardiac arrest (CA) and **B)** anaesthesia-attributable CA.

A) left - incidences of perioperative paediatric CA (2008-2013 vs 2014-2016); right - annual incidences of perioperative paediatric CA (2008-2016)

B) left - incidences of anaesthesia-attributable paediatric CA (2008-2013 vs 2014-2016); right - annual incidences of anaesthesia-attributable paediatric CA (2008-2016)

Figure 2

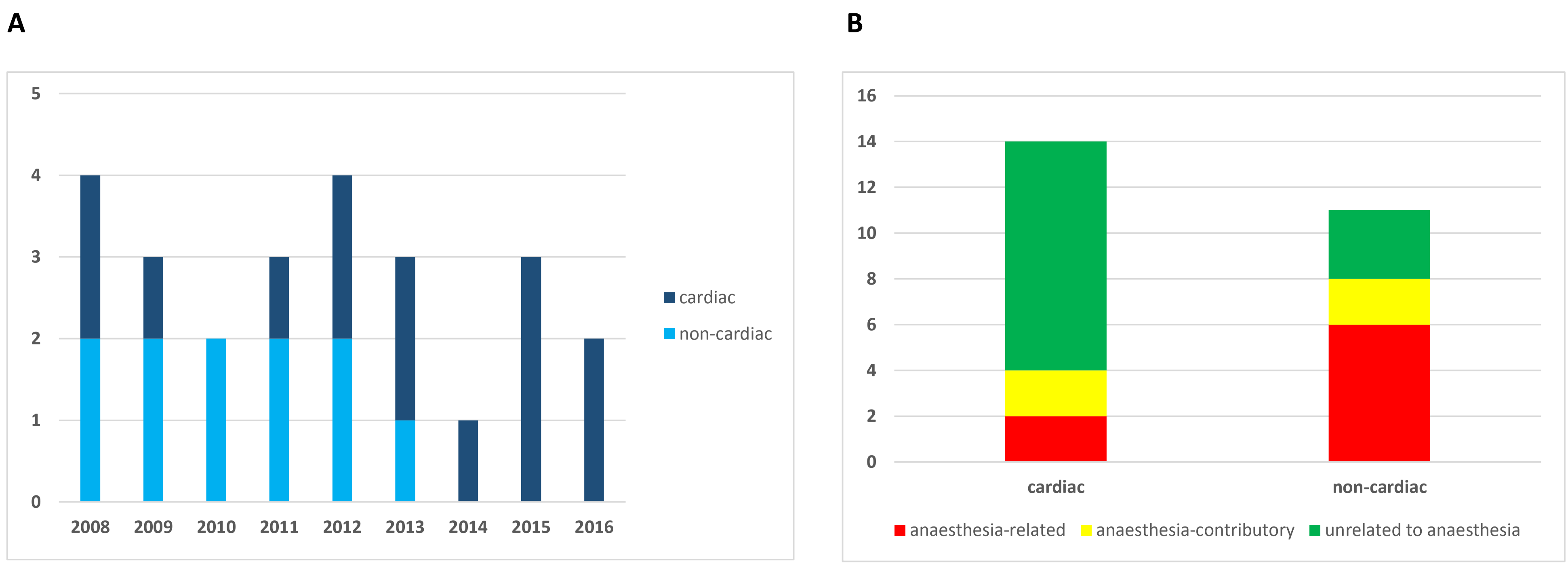

Figure 2 Numbers of perioperative paediatric cardiac arrests (CAs) in children undergoing cardiac procedures (cardiac surgery or cardiac catheterisation) (n=25).
Figure 2A shows the annual proportions of CAs in cardiac and non-cardiac procedures during the study period (2008-2016).
Figure 2B shows the proportions of anaesthesia-related, anaesthesia-contributory, and anaesthesia-unrelated CAs in cardiac patients (left column) and non-cardiac patients (right column) throughout the study period (2008-2016).

Figure 3

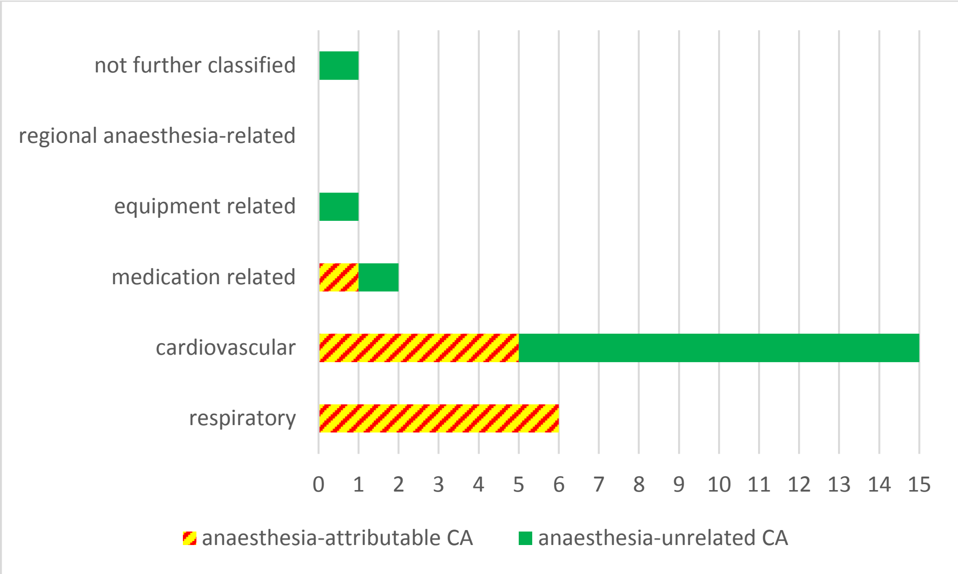

Figure 3 Distribution of primary adverse events leading to perioperative cardiac arrest (CA) in the subgroups of anaesthesia-attributable CA and CA unrelated to anaesthesia.

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Paed_CA_Tab Supp_1_final.pdf