

Incidence and Outcome of Anaphylaxis in Cardiac Surgical Patients

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ABSTRACT

Introduction: Anaphylaxis is a rare but serious and potentially fatal complication of anesthesia. Little is known about the incidence and outcome of anaphylaxis in cardiac surgical patients, which we aimed to investigate.

Methods: This was a 21-year retrospective study of cardiac surgical patients at Manchester Royal Infirmary, Manchester Foundation Trust, Manchester, UK.

Results: A total of 19 cases of anaphylaxis were reported among 17,589 patients (0.108%) undergoing cardiac surgery. The majority (15/19) occurred before cardiopulmonary bypass (CPB), mostly during or within 30 min after the induction of anesthesia (10/19). Two occurred within 15 min of going onto CPB. Of these 17 cases, 11 were abandoned, and 6 proceeded. The severity of reactions in the patients who proceeded ranged from grade II to grade IV of the Ring and Messmer classification. Two cases occurred after the completion of surgery. All patients survived to 90 days. However, this did not appear to be related to CPB or protamine as most of the reactions occurred before CPB. Instead, the most common causative agents were gelofusine, antibiotics, muscle relaxants, and chlorhexidine. In 6 cases, surgery proceeded despite the anaphylaxis, in 11 cases the surgery was postponed, and in 2 cases the procedure had already been completed.

Conclusion: As all patients survived, our results provide preliminary support for proceeding with surgery although we cannot speculate on the likely outcomes of patients who were postponed, had their surgery proceeded. Based on our data, the incidence of anaphylaxis in cardiac surgical patients may be 10–20 times higher than in the general surgical population.

Keywords: Cardiopulmonary bypass, mechanical circulatory support, resuscitation, shock

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Submitted: 12-Sep-2021 Accepted: 25-Jan-2022 Published: 05-Jul-2022

INTRODUCTION

Systemic hypersensitivity is the main feature of anaphylaxis and can vary from relatively minor to severe, resulting in a potentially life-threatening reaction that can indeed be fatal.^[1]

The onset of anaphylaxis is often rapid, frequently occurring within a few minutes of exposure and usually within an hour. IgE antibodies bind to receptors on mast cells and basophils and cause degranulation with the release of inflammatory and vasoactive mediators. These substances, especially histamine, lead to profound

Access this article online	
Quick Response Code:	Website: www.annals.in
	DOI: 10.4103/aca.aca_170_21

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How to cite this article: Norawat R, Vohra A, Parkes A, O'Keefe NJ, Anipindi S, Maybauer MO. Incidence and outcome of anaphylaxis in cardiac surgical patients. *Ann Card Anaesth* 2022;25:323-9.

vasodilation and severe hypotension, increased vascular permeability, bronchoconstriction, and cutaneous features such as erythema and urticaria.^[2,3]

The incidence of anaphylaxis related to anesthesia is difficult to calculate, in part due to variability in diagnosis and investigation, as well as difficulties in reporting. A recent United Kingdom (UK) national audit estimated the incidence to be approximately about 1:10,000 which was similar to other published series, which have estimated incidences between 1:6,000 and 1:20,000.^[4]

In cardiac surgical patients, the incidence of anaphylaxis is still unknown. However, the administration of multiple potential triggers exposes patients to a potentially higher rate of anaphylaxis compared to other surgical populations. For example, the use of muscle relaxants, antibiotics, and antifibrinolytic agents is common,^[5] and central venous and urinary catheter insertions can be a source of chlorhexidine exposure. Heparin and subsequently protamine are also used, and the cardiopulmonary bypass (CPB) circuit may be primed by gelatine-containing solutions. All of these are potential additional triggers for anaphylaxis.^[6,7] The aim of this study was to investigate the incidence of anaphylaxis in our cardiac surgical patients, the severity of the reactions, the decisions on whether to proceed with the planned surgery and the 90-day survival.

MATERIALS AND METHODS

This retrospective study was conducted as an internal registered audit (audit # 7421, Manchester University NHS Foundation Trust (MFT)). This service review as determined by the National Health Service (NHS) health research authority decision tool did not require further ethics approval.^[8] Anonymized electronic data were collected over a 21-year period from 1st January 1997 to 31st December 2017. This study included all adult patients (18 years or older) who underwent cardiac surgery at MFT during this period. The information about the true positive cases who developed acute intraoperative anaphylactic reactions was obtained retrospectively from referrals to our Anesthetic Reaction Clinic (ARC) as well as through the Audit Department by searching the word “anaphylaxis” within the coding system.

Clinical data collection

Demographics (age, gender), baseline characteristics (American Society of Anesthesiologists (ASA) physical status, type of surgery), and details of the reaction including suspected allergens, hemodynamic parameters, the severity of the reaction, and treatment received were obtained. We

also obtained information about the timing of the reaction in relation to the onset of anesthesia or CPB. The severity of the reaction was graded according to the Ring and Messmer classification.^[9] Severity grading ranges from I through IV with Grade I being the presence of cutaneous symptoms and Grade IV being circulatory inefficacy, leading to cardiac arrest with or without the inability to ventilate. We also obtained data on the decision to continue with the planned surgery. The primary outcome measured was 90-day survival after the event.

Diagnosis of anaphylaxis and the causative agent

For clinical suspicion of anaphylaxis, blood samples for serum tryptase at three-time points (within 1 h, 2–4 h, and at 24 h) of the event were measured. A dynamic rise in tryptase was deemed to be a marker supporting the diagnosis of anaphylaxis.

The confirmation of the culprit agent was based on the following standard battery of tests:

Skin prick test (SPT)

SPT is a primary method of testing immediate IgE-mediated allergic reactions. SPT was performed after checking all the prerequisites with histamine control positive and negative control. The test was considered positive if wheal was >3 mm with histamine control or >6 mm with negative control. Various anesthetic agents including opioids, induction agents, local anesthetics, muscle relaxants, gelofusine, antibiotics, latex, chlorhexidine, and other agents used during the surgery were tested by SPT.

Intradermal injection test (IDT)

IDT included anesthetic drugs, opioids, muscle relaxants, antibiotics, latex, chlorhexidine, and any other drugs given to the patients (including aprotinin or tranexamic acid). IDT is performed to identify for both immediate IgE-mediated and delayed-type hypersensitivity reactions. A positive IDT response was defined as a greater than 6 mm wheal at a 1:100 dilution of extract.

IgE-mediated response to specific agents was tested on some of the cases. For example, all three tests were not always performed for every case. This was in order to minimize patient risk. For example, a positive skin prick test was not always followed by intradermal injection.

RESULTS

A total of 19 cases of perioperative anaphylaxis were referred to the Anesthetic Reaction Clinic out of 17,589 patients who underwent cardiac surgery during this 21-year period. This indicates an incidence of 0.108%

in our cardiac surgical patients. Out of the 19 reported cases, there were 13 male and 6 female with a mean age of 64 years (ranging from 45 to 77 years). Complete perioperative records were not available for all patients, but sufficient data were available for analysis in all cases. All incidents were followed up internally with full patient disclosure.

Seven cases had a history of allergy; penicillin in four cases, latex in one, chlorhexidine in one, and statins in one. Two of these cases inadvertently received a known allergenic agent. One patient with chlorhexidine allergy unknowingly had a chlorhexidine-impregnated central venous catheter inserted. The other received co-amoxiclav in the background of penicillin allergy.

A summary of all cases is shown in Table 1. All patients survived more than 90 days after the anaphylactic event. A total of 15 of the 19 cases (79%) had reactions before the commencement of CPB. Ten (67%) of these reactions occurred within 30 min of induction of anesthesia. A total of 2/19 (10.5%) occurred within 15 min of going onto CPB both were due to gelofusine. One of these two proceeded to the completion of the surgery, and the other had a surgery postponed. Two cases had reactions after completion of surgery: one before leaving the operating

room (unknown agent), and one in the cardiac intensive care unit (CICU) associated with a blood product.

Overall, of the 17 cases with reactions before commencement or completion of the cardiac surgical procedure, six proceeded to completion of the planned surgery. The remaining cases were abandoned, one despite the commencement of CPB. The abandoned cases had their surgery postponed between 1 day and 18 months after the anaphylaxis event.

Of the 13 cases where the causative agents were identified, co-amoxiclav and other antibiotics were responsible in 3/13 (23%). This was associated with Grade II anaphylaxis in two of the cases and Grade III anaphylaxis in one case. Chlorhexidine was found in 3/13 (23%) cases. Two cases were associated with chlorhexidine-impregnated gel used during urinary catheterization and one case of chlorhexidine-impregnated central venous catheter. This resulted in Grade III reactions in two cases and Grade IV reactions in one case. Gelofusine infusion was found as causative in 4/13 (31%) cases. Gelofusine anaphylaxis resulted in Grade III reactions in three cases and Grade IV reactions in one case. Muscle relaxants were found in 3/13 (23%). Pancuronium anaphylaxis caused a Grade II reaction in one case. Rocuronium was associated with one

Table 1: Characteristics of anaphylactic reactions

Series number	H/O Allergy	Allergen causing reaction	Onset time	CPR	Grade of Severity	Proceed to surgery?	Hospital stay primary op	Time to re-operation	Hospital stay second op
1	NKDA	Co-amoxiclav	70 min. PI	N	II	N	1	36 days	15
2	Penicillin	Blood products	Post op CICU	N	II	Y	12	-	-
3	Penicillin	Co-amoxiclav	40 min. PI	N	II	N	2	5 months	9
4	NKDA	Co-amoxiclav or tranexamic acid	41 min. PI	N	II	Y	7	-	-
5	NKDA	Pancuronium	2 min. PI	N	II	N	?	1.5 months	?
6	Latex	Chlorhexidine or latex	28 min. PI	N	III	N	2	2 months	5
7	NKDA	Penicillin	2 min. PI	N	III	N	36	14 months	14
8	NKDA	Co-amoxiclav	51 min. PI	N	III	N	3	6 day	5
9	NKDA	Chlorhexidine	12 min. PI	N	III	N	1	3 months	7
10	Penicillin	Unknown potentially Chlorhexidine	31 min. PI	N	III	N	3	1.5 months	6
11	Statins	Gelofusine	11 min. PI	N	III	Y	10	-	-
12	NKDA	Flucloxacillin or pancuronium	Post op OR	N	III	Y	?	-	-
13	NKDA	Gelofusine	14 min. PI	N	III	Y	6	-	-
14	NKDA	Gelofusine	11 min. onto CPB	N	III	Y	10	-	-
15	Penicillin	Rocuronium	5 min. PI	Y	IV	N	8*	4 days	NDH
16	Chlorhexidine	Chlorhexidine	23 min. PI	Y	IV	N	7*	1 day	NDH
17	NKDA	Suxamethonium	7 min. PI	Y	IV	Y	?	-	-
18	NKDA	Gelofusine	13 min. onto CPB	N	IV	N	4	18 months	7
19	NKDA	Gelofusine or rocuronium	30 min PI	Y	IV	Y	26	-	-

NKDA – No known drug allergies, PI - Post induction, CICU – Cardiac intensive care unit, CPR - Cardiopulmonary resuscitation, NDH - Not discharged home, CPB - Cardiopulmonary bypass, OR - Operating theatre, N – No, Y - Yes. ? indicates missing data. * indicates two cases who were cancelled at time of event but not discharged home until having their operation

Table 2: Diagnostic tests

Series number	Operation	Allergy trigger	Serial tryptase	Skin prick test	Intra dermal test	IgE
1	MVR	Co-amoxiclav	Dynamic tryptase rise	Negative to all	Positive to co-amoxiclav	Not done
2	CABG+AVR	Blood products	Not done	Not done	Not done	No rise
3	CABG+AVR	Co-amoxiclav	No rise	Negative to all	Positive to co-amoxiclav	Positive to amoxicillin
4	CABG	Co-amoxiclav or tranexamic acid	Dynamic tryptase rise	Negative to all	Positive to tranexamic acid	Positive to amoxicillin
5	CABG	Pancuronium	Not done	Positive to Pancuronium	Not done	Not done
6	CABG	Chlorhexidine or latex	Dynamic tryptase rise	Positive chlorhexidine & latex	Positive to chlorhexidine & latex	Positive to chlorhexidine
7	Redo-CABG	Penicillin	Dynamic tryptase rise	Negative to all	Negative to all	Positive to penicillin
8	Redo-CABG	Co-amoxiclav	Dynamic tryptase rise	Negative to all	Negative to all	Not done
9	AVR	Chlorhexidine	Dynamic tryptase rise	Positive to chlorhexidine	Not done	Positive to chlorhexidine
10	CABG	Unknown (potentially chlorhexidine)	Dynamic tryptase rise	Negative to all	Negative to all	All negative
11	AVR	Gelofusine	Dynamic tryptase rise	Negative to all	Positive to gelofusine	Positive to gelofusine
12	CABG+AVR	Flucloxacillin or pancuronium	Not done	Positive to flucloxacillin & pancuronium	Not done	Not done
13	AVR	Gelofusine	Dynamic tryptase rise	Negative to all	Positive to gelofusine	Positive to gelofusine
14	CABG	Gelofusine	Dynamic tryptase rise	Negative to all	Positive to gelofusine	Not done
15	CABG	Rocuronium	Dynamic tryptase rise	Positive to rocuronium & suxamethonium	Not done	Positive to rocuronium
16	AVR	Chlorhexidine	Dynamic tryptase rise	Positive to chlorhexidine	Not done	Positive to chlorhexidine
17	CABG	Suxamethonium	Dynamic tryptase rise	Positive to suxamethonium	Not done	Not done
18	MVR+TVR	Gelofusine	Dynamic tryptase rise	Positive to gelofusine	Positive to gelofusine	Positive to gelofusine
19	CABG	Gelofusine or rocuronium	Dynamic tryptase rise	Negative to all	Equivocal to rocuronium and gelofusine	Mild rise to gelofusine

MVR - Mitral valve replacement, CABG - Coronary artery bypass grafting, AVR - Aortic valve replacement, TVR - Tricuspid valve replacement

Grade IV reaction. Suxamethonium was associated with a Grade IV reaction.

Interestingly, Grade IV reactions occurred in 5/19 (26%) of cases. Four occurred after anesthesia, one after going onto CPB. All four cases that were not on CPB at the onset of Grade IV anaphylaxis required CPR. Two of the five cases (40%) proceeded to completion. The one case that was already on CPB had the operation postponed.

Not all reasons for postponement could be investigated due to a lack of documentation. All patients were transferred to CICU for mechanical ventilation, except one case, who had an early reaction without the need for tracheal intubation. A total of 11/19 (58%) cases had their operations postponed. Three of four cases with Grade II reactions were postponed, compared to five of eight with Grade III reactions, and three of five with Grade IV reactions.

The delay between cancellation and reoperation ranged from 1 day to 18 months.

The data on hospital stay, where available, are presented in Table 1.

DISCUSSION

Our study identified 19 cases who had anaphylaxis out of 17,589 patients who underwent cardiac surgery in our institution over two decades. A summary of diagnostic tests done in all cases are shown in [Table 2]. A total of 15 of the 19 cases had a dynamic rise in tryptase and at least one or more positive postevent tests (SPT, IDT, IgE). One case had a dynamic tryptase rise and equivocal IDT and IgE tests for rocuronium or gelofusine. Two cases had a dynamic tryptase rise without any positive postevent tests but were reported as reactions to chlorhexidine and coamoxiclav. In one case, presumed to have reacted to blood products, dynamic tryptase was not done, and there was no positive postevent test for drugs or fluids given to the patient at the time of the event. However, we have not excluded any of these cases in our discussion because of their clinical presentation and clinical significance. We realize that this

affects our percentage sub-calculations to specific agents when the total numbers are small. However, it should not detract from our broad evaluation of causation, intervention, and treatment outcomes in order to help us to inform us about ways to improve the care of such patients in the future.

The severity of anaphylaxis in our cardiac surgical patients appeared to have little or no influence on the decision to proceed or abandon planned surgery although given the small numbers, this could not be assessed in this study. However, proceeding or abandonment of surgery did not influence mortality because all cases survived. It is common practice to defer nonurgent surgery where possible if an anaphylactic reaction is suspected. However, it is debatable whether proceeding with surgery is likely to lead to a worse outcome following an anaphylactic reaction. It is also uncertain if deferring surgery causes harm by leading to excessive physiological strain or deterioration of their underlying cardiac condition.^[10] One has to consider the risk of secondary injury from a potential CPB-related systemic inflammatory response syndrome (SIRS) compounding the vascular leakage due to anaphylaxis.^[11-13] This could make pulmonary or cerebral edema more likely. On the other hand, cardiovascular stability can be achieved by establishing the patient on CPB.^[10] Anaphylaxis commencing during CPB was rare in our cohort.

If the initial management and stabilization of the reaction have been successful, uncertainty remains on the decisions to proceed or abandon surgery. This was particularly important in our group of nine cases with Grade III reactions. Four out of the nine completed surgery. This did not appear to result in either increased intraoperative epinephrine doses; intra- and postoperative vasopressor requirements; nor mean postoperative ventilation time in comparison to those cases in which the cardiac surgical procedure was abandoned. There was also no sign of any increased pulmonary, neurological, or renal impairment postoperatively. Similarly, two cases with Grade IV reactions had their surgery completed, without any postoperative complications. However, it is not possible to speculate on the outcomes for the cases that were postponed, had their surgery proceeded.

During cardiac surgery, patients are routinely exposed to multiple agents, including induction agents, analgesic drugs, neuromuscular blocking agents (NMBA), antibiotics, blood products, heparin or alternative anticoagulants, antifibrinolytic agents such as aprotinin or tranexamic acid, latex, protamine, intravascular volume expanders, and chlorhexidine, all of which are potential triggers

for anaphylaxis.^[5,14-16] The causative agents in our group included gelofusine, coamoxiclav, chlorhexidine, muscle relaxants, and blood products although the causative agent could not be confirmed in three cases and equivocal and inconclusive results in three other cases.

Calculating the true incidence of anaphylaxis in the perioperative period is difficult. Most reporting is retrospective, and case series are rarely collated. There is also considerable variability in the diagnosis and investigation of suspected reactions. During general surgery, most published series have estimated the incidence of perioperative anaphylaxis as between 1:6,000 and 20,000.^[17] Most recent findings of the “6th National Audit Project (NAP6): Perioperative Anaphylaxis” in the UK, suggest the risk of anaphylaxis is approximately 1:10,000 procedures, with a mortality rate of 3.8%.^[4] Whether cardiac surgical patients are at increased risk of perioperative anaphylaxis because of the multiple drugs administered or CPB, remains uncertain.

Levy and colleagues reported eight reactions in 1743 patients (1:200) in their cardiac surgery patients. The causative agents were identified as protamine, vancomycin, blood products, and metocurine.^[6] However, these data included anaphylactoid reactions, and it is possible that the reactions attributed to both blood and vancomycin could have been nonallergic in nature. Nevertheless, even if even 1:4 of the 8 reactions were anaphylaxis, the incidence would be >1:1,000. Ford and colleagues interrogated their database of 1346 patients and identified 23 patients (1.7%) that developed anaphylaxis during cardiac surgery.^[7] The triggers identified in this series were antibiotics (30%), colloid-based fluids (26%), muscle relaxants (17%), blood products (8.6%), protamine (13%), and morphine (4.3%).

Our study, like the studies by Levy *et al.*^[6] and Ford *et al.*,^[7] suggests that the incidence of anaphylaxis in cardiac surgical patients may be more than 10 times higher than in the general surgical population (0.01%).^[4] The reasons for the higher incidence are unclear. However, they do not appear to relate to CPB because most reactions occurred before CPB or after separation from CPB. Similarly, we did not identify any anaphylactic reactions to protamine. NAP6 has shown that antibiotics are the most common trigger for anaphylaxis, related to anesthesia as a whole, being responsible for 47% of cases.^[4] They found that teicoplanin was associated with a 17-fold greater risk than cefuroxime, and 2-fold greater than co-amoxiclav for causing adverse reactions. Antibiotics are followed by muscle relaxants (33%) and chlorhexidine (9%) as the most common causes.^[4] Interestingly, we found that the

causative agents in our cardiac group were similar to those noted in NAP 6 and included antibiotics (23%), muscle relaxants (23%), and gelatin (31%).^{14]}

It is possible that some cases of postoperative hypotension attributed to post-CPB vasoplegia and treated with vasopressors in our 17,589 patients could potentially have been a reaction to protamine and were overlooked, which may explain why our case series did not include protamine as a cause of anaphylaxis. If this were true, the true incidence of anaphylaxis related to cardiac surgery may even be higher. Indeed, the recognition and subsequent diagnosis of anaphylaxis are potentially more difficult in a cardiac surgical population than in a general surgical population. The classical cardiovascular features of anaphylaxis of severe hypotension and tachycardia could be attributed to their underlying cardiac disease. Cutaneous features of a reaction such as erythema and urticaria may be missed as patients are invariably covered by surgical drapes throughout their surgery, and these signs may have resolved and therefore be missed before the end of the procedure. Similarly, during CPB, whilst we may see unexpectedly high requirements of norepinephrine to maintain mean arterial pressure, hypoxia during anaphylaxis may not be seen because oxygenation is maintained with the CPB oxygenator.

Sadleir and colleagues^{110]} described the severity of anaphylactic reactions in 223 patients in whom (“general”) surgery proceeded. They found that patients with severe reactions (Grade III or IV) were more likely to have their surgery abandoned when compared with those suffering less severe reactions (I or II). This is in contrast with our own experience where the more severe reactions were more likely to go ahead with their planned surgery. They suggested that additional factors, perhaps less relevant to cardiac surgery, such as prone positioning or anticipated significant surgical bleeding may impair the intraoperative management of a reaction and so influence the decision to proceed.^{110]} A potential advantage of cardiac surgery is easy access to CPB as a potential aid to provide cardiovascular stability and given the results of our study, leads us to suggest considering abandoning nonessential cardiac surgery only in patients with Grade I and II reactions who will not require level III critical care postreaction. We found proceeding swiftly to CPB in several patients with Grade III and IV reactions to achieve initial cardiovascular stability did not appear to worsen the outcome. Hemodynamic instability in the presence of significant coronary artery disease is a high risk for myocardial infarction, and establishing stability on CPB is likely to be protective here. However, all our patients survived, including those in whom surgery was postponed.

In the light of our findings, we have changed our practice to now avoid unnecessary exposure to potential allergens. We have stopped the routine use of gelatine-containing fluids at induction of anesthesia or adding these as part of the CPB prime. We have also discontinued the use of chlorhexidine-impregnated lubricant gels, and we no longer routinely use chlorhexidine-impregnated central venous catheters. While antibiotics are obviously required, the actual regimen has changed over time. Our current choice is flucloxacillin with gentamicin.

In conclusion, we found a 10- to 20-fold higher incidence of anaphylaxis in our cardiac surgical population compared with published data for general surgical patients. However, this did not appear to be related to CPB or protamine, as most of the reactions occurred before CPB. Instead, the most common causative agents were gelofusine, antibiotics, muscle relaxants, and chlorhexidine. In 6 cases, surgery proceeded despite the anaphylaxis and in 11 cases the surgery was postponed (in two cases the procedure had already been completed). As all patients survived, our results provide preliminary support for proceeding with surgery although we cannot speculate on the likely outcomes of patients who were postponed, had their surgery proceeded.

Acknowledgments

The authors thank all cardiac surgeons and anesthesiologists, the nursing staff, the and team of the CICU, all support staff, and the staff of the Anesthetic Reaction Clinic for their contributions in managing and investigating these patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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