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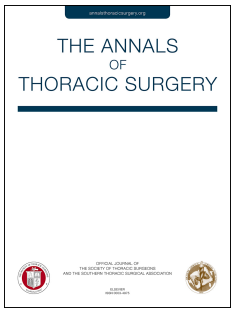

The characteristics of postoperative mediastinitis during the changing phases of cardiac surgery

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The characteristics of postoperative mediastinitis during the changing phases of cardiac surgery

Running head: Postoperative mediastinitis in 1990-2018

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Classifications: Mediastinal infection, Coronary artery bypass, CABG, Coronary stents, PCI, Heart valve repair, Surgery, complications

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Abstract

Background: Mediastinitis is a serious complication of open-heart surgery associated with high mortality, considerable healthcare costs and prolonged hospital stay. We examined characteristics and incidence of mediastinitis during 29 years when indications and patient material have been in a process of change.

Methods: A retrospective population-based study comprising all mediastinitis patients over 16 years of age after open-heart surgery between 1990-2018 from a population of 1.7 million. Patient records of 50 mediastinitis patients from 2004-2014 were reviewed and compared to 120 patients from 1990-1999.

Results: Annual mediastinitis rate varied 0-1.5 % with a decreasing trend - from a level exceeding 1.2 % to about 0.3 % - over the study period. In 2004-2014 patients with mediastinitis were older, more often smokers, had more often diabetes and renal insufficiency than in 1990-1999. No difference in length of hospital treatment, antibiotic prophylaxis or treatment, ICU treatment or mortality was observed between 1990-1999 and 2004-2014. CABG became less common and valve replacement and hybrid operations more common among operations leading to mediastinitis. *Staphylococcus aureus* increased (from 25% to 56%, $p = 0.005$) while coagulase negative staphylococci (46% to 23%, $p < 0.001$) and Gram-negative bacteria (18% to 12%, $p = 0.033$) decreased as causative agents. Surgery for mediastinitis remained similar except introduction of vacuum assisted closure treatment.

Conclusions: The rate of mediastinitis decreased during these 29 years. No difference in 30-day mortality in mediastinitis was seen, 0.9 % in 1990-1999 and 2.0 % in 2004-2014.

242 words

BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CDC	Centers of Disease Control and Prevention
CoNS	Coagulase Negative Staphylococci
COPD	Chronic Obstructive Pulmonary Disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease

Abbreviations

HUCH	Helsinki University Central Hospital
ICU	Intensive Care Unit
IQR	Interquartile range
MRSA	Methicillin Resistant Staphylococcus Aureus
PCI	Percutaneous Coronary Intervention
VAC	Vacuum Assisted Closure

Mediastinitis is a serious deep infection complication after open-heart surgery which occurs in 0.3-4.2 % of operations[1,1-10]. It is associated with significant mortality between 7.7 - 33 % [1-4,6,11,12], prolonged hospitalization, higher healthcare costs, and decreased long-term survival [10,13,14].

New less invasive methods to treat coronary artery disease and valve diseases have been developed and increasingly used [15]. Today most of the coronary artery disease patients are treated by percutaneous coronary intervention (PCI), balloon plasty or stenting in Helsinki University Central Hospital (HUCH). The annual number of coronary artery by-pass grafting has decreased from 1200 to average 500 operations, while the number of annual PCI procedures have increased to over 3000. Transcatheter aortic valve implantation started in 2008. The number of these procedures has increased quickly and now they are more common than open-heart operations. Furthermore, mitral valve leakage has corrected via minithoracotomy since 2007. The use of new methods has changed the characteristics of the patient material. Average age of patients who underwent cardiac surgery has increased and they have had more co-morbidities[16].

The most common causative agents in mediastinitis are *Staphylococcus aureus*, coagulase-negative staphylococci and aerobic gram-negative bacteria[6]. Antimicrobial resistance among them has become more common which in many countries has seen especially among *S. aureus*[17]. The aim of this population-based study was to track progress in the incidence and management of postoperative mediastinitis over two separate time periods, namely 1990-1999 and 2004-2014.

Patients and Methods

We identified from the HUCH hospital register of operations all patients over 16 years old who underwent coronary artery bypass grafting (CABG) or valvular operation and from the register of healthcare-associated infections all patients who developed mediastinitis between October 2004 and October 2014. HUCH serves as the only tertiary care cardiac surgery center for a population of over 1.7 million (population of Finland is 5.5 million). Diagnosis of postoperative mediastinitis was based on modified criteria of the Centers for Disease Control and Prevention (CDC)[18], including at least one

of the following: 1) patient had organisms cultured from mediastinal tissue/fluid, 2) evidence of mediastinitis on gross anatomical/histopathological examination, 3) at least one of the following symptoms: fever (>38°C), chest pain or sternal instability and purulent drainage from mediastinal area or mediastinal widening on imaging.

Patient records on those who had mediastinitis between October 2004 and October 2014 were reviewed from electronic patient records. We included patient data from an earlier study by Eklund et al[1] done with similar setup in the same hospital and catchment area between January 1990 and December 1999. Between January 2000 and September 2004 and 2015-2018 only the amount of annual cardiac surgeries and mediastinitis were used (Figure 1).

The following preoperative information was recorded for each patient: sex, age, McCabe score of underlying diseases[19], preoperative hospital care in days, diabetes (as classified by the World Health Organization), smoking (during the prior 3 months of the operation), chronic obstructive pulmonary disease (COPD, classification according the GOLD-system[20]), renal insufficiency (plasma creatinine over 100 µmol/l on the day preceding the operation), Body Mass Index (BMI), left ventricular ejection fraction and ASA-class[21]. Information about the operation included: duration, adequate antibiotic prophylaxis (target 30-60 min prior to the operation) and type either as emergency, primary or reoperation due to a complication.

For postoperative phase, we recorded the following: length of antimicrobial treatment, surgical treatment (only revision, revision and refixation, mediastinal irrigation, vacuum assisted closure therapy (VAC), flap reconstruction, wire removal after or at the end of the treatment), duration of ventilator and intensive care unit (ICU) treatment and use of tracheostomy.

IBM SPSS 24 was used for the statistical analyses. Categorical variables were summarized using counts and percentages. Continuous variables were summarized using mean, standard deviation, median, first and third quartile, min and max values. A *p* value less than 0.05 was considered statistically significant. Continuous variables were compared with independent samples T-test or Mann-Whitney's test, proportions with Chi-square test. Change in the incidence of mediastinitis over time was analysed with Chi-square test for linear trend.

Results

Study population and cases of mediastinitis

The annual amount of cardiac operations has changed during the study period (Figure 1). In 1990, 683 operations were performed with nine cases of mediastinitis (incidence 1.3%). The annual amount of cardiac operations increased until 1999 (1534 operations). In 1999–2000 PCI frequency exceeded the annual numbers of CABG which dropped from its highest over 1200 annual operations in 1998 to 500 in 2001. Interestingly, the number of open-heart operations has since then been increasing (841 in 2007 and 1199 in 2014). During the study period, the incidence of mediastinitis varied from 0% in 2014 to 1.5% in 1991. The average proportion of patients with mediastinitis decreased during study periods 1990-1999, 2000-2003 and 2004-2014 were 0.97 %, 0.85 % and 0.49 %, respectively ($p < 0.01$).

Patients with postoperative mediastinitis were significantly older during 2004–2014 (mean age 65.8±9.1 years) in comparison to 1990–1999 (59.6±9.9 years, $p < 0.001$, Table 1). More than 80% of patients with mediastinitis were male in both study periods and there was no difference in the BMI between 1990–1999 and 2004-2014. Smoking was significantly more common in 1990-1999 (68.9%) as compared to 2004-2014 (38.0%, $p < 0.001$). Preoperative hospital stay was similar (median 2.0 vs 1.0 days, $p = 0.972$) and most patients received adequate antibiotic prophylaxis (65.7% vs 61.9%, $p = 0.584$) during 1990–1999 and 2004–2014, respectively.

From 1990–1999 to 2004–2014 the proportion of plain CABG decreased significantly, from 83.3% to 54.0% ($p = 0.011$, Table 1) among the operations that led to mediastinitis. However, more valve replacements (22.0% vs 9.2%, $p = 0.043$) and hybrid operations (valve replacement with CABG, 14.0% vs 4.2%, $p = 0.051$) were performed during 2004-2014 among patients with mediastinitis as compared to 1990–1999. No difference in the median operation time (210 vs 241 minutes, $p = 0.185$) was detected between 1990–1999 and 2004–2014.

Microbiological etiology

Time from operation to diagnosis of mediastinitis increased from 1990-1999 to 2004-2014 (median 12 vs 16 days, $p = 0.022$). During 1990-1999, microbiological etiology of mediastinitis was confirmed by culture from 109/120 (91%) and during 2004 - 2014 from 35/50 (70%) patients. Microbiological diagnosis was based mainly on wound or mediastinal cultures (Table 2). Minority of the patients were bacteremic in both periods (20% vs 30%, $p = 0.028$). Gram-positive bacteria constituted majority of microbiological findings in both 1990–1999 (82%) and 2004–2014 (89%). However, within 1990–1999, the most common pathogens were coagulase negative staphylococci (CoNS, 46% of all isolates) and within 2004–2014 *Staphylococcus aureus* (56% of isolates) (Table 2). No cases with methicillin resistant *Staphylococcus aureus* (MRSA) were detected. The proportion of Gram-negative bacteria in microbiological cultures decreased significantly, from 18% during 1990-1999 to 12% during 2004-2014 ($p = 0.033$).

The incidence of mediastinitis peaked in 2007 but the microbiological findings during that year showed no single causative agent: *Staphylococcus aureus* constituted 31%, CoNS 15% and enterococci 15% of isolates in 2007.

Treatment and outcome

During both 1990–1999 and 2004-2014 majority of patients were treated with mediastinal revision, irrigation and refixation but flap reconstructions were rarely needed (Table 3). During 2004-2014 mediastinitis was treated significantly more often with VAC (10.0% vs 0.0%, p = 0.024) as compared to 1990-1999. During 2004-2014, the median length of antimicrobial treatment was 182 days (minimum 10 ~~days~~, maximum 401 days, IQR25 98 days and IQR75 252 days). There was no difference in either short term (30 days) or long-term (1 year) mortality between 1990–1999 and 2004-2014 (Table 1).

Comment

Our study showed that the number of open-heart operations decreased after 2003 but became more common again towards the later part of the observation period in 2010's. The annual postoperative mediastinitis rate was 0.76% during the whole observation period and varied from 0 to 1.5% with a significant decreasing trend between 1990–2018 ($p < 0.01$) especially towards the last years of the study. Our study doesn't reveal a clear reason for this trend. Patients with mediastinitis in 2004-2014 were significantly older, less often smokers and they had less often only CABG operation as compared to patients with mediastinitis in 1990-1999. No difference in other patient characteristics or treatment, like antibiotic prophylaxis, length of ICU stay or ventilator days was seen between 1990–1999 and 2004-2014. Majority of all mediastinitis cases were caused by Gram-positive bacteria but a shift from CoNS to *S. aureus* as the most common pathogen was seen. Gram-negative bacteria were significantly less common in 2004-2014 as compared to 1990-1999.

In earlier studies made in the 1990's or 2000's, no difference in the incidence of mediastinitis (0.7–2.2% vs. 0.8–4.2%) [8,22-24] or in the average age of patients between (56–62 years vs. 56–64 years) [8,9,14] can be seen. Unlike in previous studies, we observed a significant increase in the age of mediastinitis patients from 1990-1999 to 2004-2014. Our data doesn't reveal if there has been a too strict age criteria for the operation in the earlier study period or if younger patients have been treated less invasively (with PCI) during 2004-2014. However, in 2004-2014 more complicated operations with simultaneous CABG and valvular operation were done significantly more often than during 1990-1999. We also observed a major shift in bacterial etiology from coagulase negative staphylococci to *Staphylococcus aureus*. In contrast to our results, the proportion of *S. aureus* as a causative agent decreased from 50 % to 37 % in one study looking changes in mediastinitis between 1996 to 2014 [25]. In other studies, *S. aureus* has been the most frequently reported pathogen in post-sternotomy mediastinitis[26,27]. In HUCH, vancomycin together with cefuroxime were used in the 90's as antibiotic prophylaxis and iodine was changed to ethanol and later to chlorhexidine alcohol in skin preparation. No nasal mupirocin or staphylococcal colonization testing were performed, or chlorhexidine mouth washes used. The median length of stay in hospital before operation did not differ between 1990–1999

and 2004–2014, offering no explanation to the decrease of coagulase negative staphylococci and Gram-negative bacteria among causative agents of mediastinitis.

The proportion of blood culture positive infections increased somewhat between 1990–1999 and 2004-2014 but this could be related to the increased incidence of *S. aureus*. Although the annual incidence of mediastinitis varied greatly, we observed a sharp rise in one year in 2007. A common causative agent or any other evident reason behind it couldn't be seen. The entire patient process from ward to operating room, operation site preparing, antibiotic prophylaxis and the perioperative and wound care were reviewed by the hospital infection control team in 2007 and again in 2010-2011. However, no major changes were done into any parts of the infection prevention bundle and cefuroxime was continued as the prophylactic antibiotic. Although, the causality cannot be shown the data suggests that strict adherence to the infection prevention bundle may have affected the lower mediastinitis rate in the subsequent years. Antibiotic prophylaxis was adequate in only 62% (1990-1999) and 66% (2004-204) of operations but our definition for adequacy was fairly strict and administration only 30-60 minutes before the operation was accepted. (Figure 2)

Our study is unable to compare the surgical techniques between the study periods. However, a major shift toward more complex surgery was observed among patients suffering mediastinitis in 1990-1999 to 2004-2014. Minimal invasive surgery was used first since 2007. Furthermore, admission to hospital on the operation day was initiated first 2011 and prolonged preoperative hospital stay before surgery may increase the risk of surgical site infections. Unfortunately, we were not able to retrieve data on the day of admission and the study cannot reveal its possible effect on the reduction of mediastinitis.

Somewhat surprisingly we observed no greater changes in the surgical treatment of mediastinitis between 1990–1999 and 2004-2014. Roughly one third of patients were treated without surgery in both periods. VAC was a new treatment in which sternal wires and all debris are removed, restabilization of the sternum is performed and VAC therapy is employed. Wound closure and subsequent reconstruction were performed using a pectoralis muscle plasty. VAC was introduced during 2004–2014 but it was used only in 10 % of patients. In 2004-2014, the median duration of antimicrobial treatment for mediastinitis was 182 days, which can be considered long – even though

there are no good quality comparative studies about antimicrobial treatment duration. Unfortunately, antibiotic treatment and its duration was not recorded in the first study period. It has to be noted that antibiotic treatment was longer and surgical treatment less common in our study than generally applied in treatment of mediastinitis, which might have also contributed to the higher incidence of culture-negative mediastinal infections.

Mortality in mediastinitis within 30 days was extremely low in both study periods as compared to other studies with similar patient and operation characteristics (0.9% – 2.0% in our study vs. 7.7 – 33% in other studies[1-4,6,11,12]). The study was made in the low antibiotic resistance area [28] and no cases due to MRSA were seen which may partly explain the low mortality rate.

Our study has strengths in its population-based set up and it included all patients coming from the same catchment area and they were all operated in the same hospital. Our study had also long follow-up time and there is only one study with almost equal long follow-up [25]. Although, closer patient record review was done in two separate sets, the same criteria for mediastinitis and data collection were used. The retrospective nature is the main limitation of this study. Secondly, although we have had continuous active surveillance of infections after cardiac surgery with similar criteria throughout the study period, we cannot exclude the possibility that some cases of mediastinitis might have not been noticed. Thirdly, severity of the surgical site infection was not graded by the same physician for both 1990–1999 and 2004-2014, yet the same CDC criteria were applied. Due to infrequent surgical treatment we had to use radiological criteria and the clinical presentation for mediastinitis quite often which decreased microbiological confirmation as well. Fourthly, comparison of detailed medical data of mediastinitis and all operated patients was not possible. Fifthly, we did not have access to blood transfusion data where changes could have affected the infection risk. We did not include children, heart transplants or operations on congenital heart defects.

In conclusion, the rate of postoperative mediastinitis decreased significantly during the study period. The 30-day mortality in mediastinitis remained exceptionally low and *Staphylococcus aureus* took the place of the most common causative agent from coagulase negative staphylococci.

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Table 1: Characteristics of the patients with post-surgical mediastinitis in 1990-1999 and 2004-2014 in Helsinki University Hospital. Number of patient and (%) within groups are shown when not otherwise stated.

Variables	1990 – 1999 (n=120) [a]	2004 – 2014 (n=50)	*p* value
Age (mean +/- SD)	59.6 +/- 9.9	65.8 +/- 9.1	< 0.001
Male	99 (82.5)	41 (82.0)	0.938
BMI (mean +/- SD)	29.0 +/- 4.1	29.1 +/- 5.2	0.928
Cardiac ejection fraction	0.54 +/- 0.15	0.49 +/- 0.12	0.061
Diabetes	25 (20.8)	16 (32.0)	0.176
COPD	16 (13.3)	13 (26.0)	0.076
Renal insufficiency	5 (4.2)	8 (16.0)	0.021
Smoking	82 (68.9)	19 (38.0)	< 0.001
LOS before operation (days, median, IQR25, IQR75)	2.0, 1.0, 3.0	1.0, 1.0, 4.3	0.972
Type of operation			
Valve replacement	11 (9.2)	11 (22.0)	0.043
CABG	100 (83.3)	32 (54.0)	0.011
Valve replacement and CABG	5 (4.2)	7 (14.0)	0.051
Other	4 (3.3)	0 (0.0)	0.453
Reoperation	15 (12.5)	0 (0.0)	0.249
Adequate antibiotic prophylaxis [b]	69 (65.7)	26 (61.9)	0.722
Operation time (minutes, median, IQR25, IQR75)	210, 175, 250	241, 200, 270	0.185
Ventilator treatment over 48h	9 (7.5)	6 (12.0)	0.518
ICU treatment (days, median, IQR25, IQR75)	2.0, 1.0, 2.8	2.0, 1.0, 4.0	0.309
Tracheostomy	3 (2.5)	1 (2.0)	0.839
30-day mortality	1 (0.9)	1 (2.0)	0.523
1-year mortality	10 (8.7)	5 (10.0)	0.729

Data are presented as number (%) or mean/median of patients.
BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LOS length of hospital treatment
[a]Eklund et al [1]
[b]Adequate antibiotic and given 30-60 min before the operation

Table 2: Microbiological findings in patients with mediastinitis after cardiac surgery grouped according to sampling site and study period either in 1990-1999 or 2004-2014. P-values are calculated between these two study periods from all samples using Chi-square test.

Microbe	Wound		Drains		Mediastinum		Blood		All		
	1990-1999[a]	2004-2014	1990-1999[a]	2004-2014	1990-1999[a]	2004-2014	1990-1999[a]	2004-2014	1990-1999[a]	2004-2014	p value
	n=109	n=24	n=36	n=2	n=67	n=11	n=24	n=15	n=236	n=52	
Gram-positive bacteria	91 (83.5)	21 (87.5)	25 (69.4)	2 (100.0)	57 (85.1)	10 (90.9)	21 (87.5)	13 (86.7)	194 (82.2)	46 (88.5)	0.216
CoNS	52 (47.7)	7 (29.2)	15 (41.7)	2 (100.0)	34 (50.8)	2 (18.2)	7 (29.2)	1 (6.7)	108 (45.8)	12 (23.1)	<0.001
S. aureus	22 (20.2)	10 (41.7)	10 (27.8)	0	14 (20.1)	8 (72.7)	13 (54.2)	11 (73.3)	59 (25.0)	29 (55.8)	0.005
Str. viridans	3 (2.8)	0	0	0	0	0	0	0	3 (1.3)	0	0.321
Enterococci	3 (2.8)	3 (12.5)	0	0	3 (4.5)	0	1 (4.2)	1 (6.7)	7 (3.0)	4 (7.7)	0.335
Cutibacter[b]	6 (5.5)	1 (4.2)	0	0	4 (6.0)	0	0	0	10 (4.2)	1 (1.9)	0.391
Other Gram-positives	5 (4.6)	0	0	0	2 (3.0)	0	0	0	7 (3.0)	0	0.278
Gram-negative bacteria	16 (14.7)	3 (12.5)	10 (27.8)	0	8 (11.9)	1 (9.1)	3 (12.5)	2 (13.3)	42 (17.8)	6 (11.5)	0.033
E. coli	2 (1.8)	0	0	0	1 (1.5)	0	1 (4.2)	0	4 (1.7)	0	0.577
Klebsiella sp.	1 (0.9)	1 (4.2)	4 (11.1)	0	3 (4.5)	0	0	0	8 (3.4)	1 (1.9)	0.278
Serratia sp.	2 (1.8)	0	0	0	0	0	1 (4.2)	2 (13.3)	3 (1.3)	2 (3.9)	0.763
Enterobacter sp.	1 (0.9)	0	1 (2.8)	0	1 (1.5)	0	1 (4.2)	0	4 (1.7)	0	0.577
Acinetobacter sp.	3 (2.8)	0	2 (5.6)	0	2 (3.0)	0	0	0	7 (3.0)	0	0.278
Pseudomonas aeruginosa	3 (2.8)	2 (8.3)	3 (8.3)	0	0	1 (9.1)	0	0	6 (2.5)	3 (5.8)	0.518
Stenotrophomonas maltophila	2 (1.8)	0	0	0	1 (1.5)	0	0	0	3 (1.3)	0	0.755
Other Gram-negatives	2 (1.8)	0	0	0	0	0	0	0	2 (0.9)	0	0.423
Mycoplasma hominis	2 (1.8)	0	1 (2.8)	0	2 (3.0)	0	0	0	5 (2.1)	0	0.448

Data are presented as number (column-%) of patients.
CoNS, coagulase negative staphylococci
[a]Eklund et al [1]
[b]Formerly Propionibacter

Table 3: Surgical treatment of patients with postoperative mediastinitis in Helsinki University Hospital catchment area between years 1990-1999 and 2004-2014

Treatment	1990 - 1999 (n=120) [a]	2004 - 2014 (n=50)	*p* value
No surgical treatment	39 (32.5)	18 (36.0)	0.662
Only wound revision	1 (0.8)	1 (2.0)	0.520
Revision and refixation	73 (60.8)	29 (58.0)	0.810
Mediastinal irrigation	64 (53.3)	31 (62.0)	0.299
VAC	0 (0.0)	5 (10.0)	0.024
Flap reconstruction	12 (10.0)	6 (12.0)	0.701
Data are presented as number (%) of patients VAC, vacuum assisted closure therapy [a]Eklund et al [1]			

Figure Legends

Figure 1: Number of operations performed and rates of mediastinitis in 1990-2018 together with the regression line in Helsinki University Hospital which takes care of all cardiac operations from a population of over 1.7 million. A significantly decreasing trend in the rate of mediastinitis was observed using Chi-square test for linear trend ($p < 0.01$). Number of annual operations are shown as bars and refer to left side y-axis. Annual rate of mediastinitis (%) is shown as the orange line and refer to right side y-axis. Linear trend is drawn as black line.

Figure 2: Timeline with changes made in the surgical or infection prevention techniques.

[a] Quality program included surgical and cardiopulmonary bypass recommendations as well as peri- and postoperative care.

[b] The entire patient process from the ward to the operating room, operation site preparing, antibiotic prophylaxis and the perioperative and wound care