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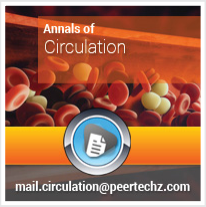

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Saad Rustum*, Felix Fleissner, Erik Beckmann, Fabio Ius, Mathias Wilhelmi, Serghei Cebotari, Axel Haverich and Issam Ismail

Division of Cardiac, Thoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany

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***Corresponding author:** Saad Rustum, MD, Carl-Neuberg Str.1, 30625 Hannover, Germany, Tel: +495115326589, Fax: +495115325404; E-mail: rustum.saad@mh-hannover.de

Felix Fleissner, Division of Cardiac, Thoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany,

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Research Article

Is There an Upper Limit to Cardiopulmonary Bypass Times?

Abstract

Background: There are no safe operations in cardiac surgery. Every operation can possibly go wrong. We therefore retrospectively evaluated all cardiac operations lasting more than 300 minutes of bypass time at our institution to evaluate outcome and factors relevant for perioperative mortality and morbidity.

Methods: We retrospectively included patients receiving cardiac operations or operations at the great vessels with cardiopulmonary bypass times above 300 minutes operated from 1/1/1996 until 12/1/2012 in our study. Patients receiving lung or heart or combined heart and lung transplantations were excluded from our study. 240 patients were included in our study. CPB times, clamp times and operation times were 356.53 ± 55.06 min, 166.18± 65.95 min, 500.47± 96.56 min respectively. Euro score of patients was 14.92 ± 15.35 (range 0.64-79.48).

Results: Intraoperative and in-hospital mortality was 11.7% (n=28) and 32.9% (n=79), respectively. Overall mortality was 50.4%. Complication rates were high. Stroke, postoperative dialysis, re-thoracotomy rates were 11.1% (n=24), 35.9% (n=78) and 30.4% (n=66), respectively.

Sex, age, infectious endocarditis, need for re-thoracotomy, CABG, aortic clamp times and postoperative dialysis predicted overall mortality in the multivariate analysis. CPB times and operation times were no independent predictors for overall mortality in this collective.

In the patients collective excluding the intraoperative deaths, multivariate analysis revealed postoperative lactate levels, amylase levels, and intraoperative need for thrombcyte concentrates and ECMO support to be predictors of mortality. The introduction of reliable ECMO support (general availability starting in 2009) resulted in a significant reduction of intraoperative mortality and overall mortality ($p<0.001$).

Conclusion: Very long CPB times due to intraoperative encountered complications can occur at any given Euroscore. They are associated with a high mortality and morbidity, however even bypass times of over 500 minutes can be survived. The introduction of the ECMO reduced intraoperative mortality however, had no impact on in-hospital mortality.

Introduction

Cardiac surgery is, despite all advances, still accompanied by a significant mortality and morbidity [1]. If catastrophic events in cardiac surgery happen, eg., Bleeding or impossibility of weaning of CPB, very long bypass times can occur. Despite improvements in bypass safety, prolonged CPB times are associated with increased mortality and morbidity [2]. In the end, if there is no other choice, the cardiac surgeon has to rely on long bypass times to finish the operation. Hence we investigated the outcome of patients at our clinic who received cardiac surgery or surgery of the great vessels with a CPB time over 300 minutes. The goal was to identify prognostic markers for survival, identify perioperative morbidities and identify the upper limit to CPB times.

Methods

We retrospectively included adult patients receiving cardiac operations or operations of the great vessels with cardiopulmonary bypass times above 300 minutes operated from 1/1/1996 until 12/1/2012 in our study. Patients receiving lung or heart or combined heart and lung transplantations were excluded from our study. 240 patients were included in our study. Euroscore of patients was 14.92 ± 15.35 (range 0.64-79.48). 95 patients (39.6%) were re-operations. Mean age was 59.29 years ± 13.3 (range 17-84 years) and 69.2% (n=166) of patients were male (Table 1). Retrospective analysis of the reason for excessive CPB times was done by evaluation of the operation protocols.

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Statistical analysis

Primary end-points were intra-operative mortality and overall mortality. Data analysis was performed using SPSS 22.0 (IBM, NY, USA) and the Categorical and continuous variables were summarized as percentages and means ± standard deviation (SD) or median with interquartile range (IQR), respectively. The independent-samples Student's *t*-test or the non-parametric Mann–Whitney *U*-test and the χ^2 or Fisher's exact tests were used for group comparisons of continuous and categorical variables, respectively. Two-tailed *P*-values ≤0.05 were considered significant. Multivariate analysis, using a forward stepwise logistic regression model, was performed to identify independent risk factors for intraoperative mortality and overall mortality. Model calibration was evaluated using the Hosmer–Lemeshow (H-L) goodness-of-fit test. A Cox regression analysis was performed to identify independent risk factors for mortality conditioned to hospital discharge. Results are reported as odds ratios (ORs) with a 95% confidence interval (CI) and corresponding *p*-value.

Results

CPB times, clamp times and operation times were 356.53 ± 55.06 min, 166.18± 65.95 min, 500.47± 96.56 min respectively (Table 2). The performed surgery and indication for surgery was heterogenous (Tables 1-3). Indication for surgery was endocardits, acute aortic and chronic aortic dissection, chronic pulmonary embolism, and myocardial tumors in 10.9% (n=26), 25.4% (n=61), 3.8% (n=9) and 1.3% (n=3), respectively.

However, the reason remained unclear in some cases (21.7%, n=52). Main indication for long CPB times was difficult surgery, bleeding, difficulties of weaning of the CPB, iatrogenic dissections and other iatrogenic complications (AV dislocation, rupture of AV integrity and alike) in 17.5%, 29.6%, 36.7%, 6.3% respectively.

Intraoperative and intrahospital mortality was 11.7% (n=28) and 32.9% (n=79), respectively. Overall mortality was 50.4% (n=121). Intraoperative blood products were administered in every patient with red packed blood cells (RBC) 13.77 ± 12.63 units, Fresh frozen plasma (FFP) 10.21 ± 8.38 units and thrombocyte concentrates (TC) 3.96 ± 3.37 units. Overall blood products were RBC, FFP and TC 24.78 ± 21.57 units, 20.78 ± 18.57 units and 10.03 ± 18.06 units, respectively (Table 4). 36 patients (15%) received extracorporal membrane oxygenatory support (ECMO) and 46 patients (19.2%) received intraaortic balloon pump (IABP). Almost all patients represented elevated liver and kidney retention parameters. Complication rates were high. Stroke, postoperative dialysis and re-thoracotomy rates were 11.1% (n=24), 35.9% (n=78) and 30.4% (n=66), respectively. Postoperative ventilation time was 140.14 ± 269.81 hours. ICU stay was 11.32 ± 16.44 days. Cause of death were heart failure, right heart failure, bleeding, multi-organ failure and cerebral cause in 17.9% (n=43), 1.3% (n=3), 3.3 (n=8), 19.6% (n=47) 1.3% (n=3), respectively.

Sex, age, infectious endocarditis, need for re-thoracotomy, CABG, aortic clamp times and postoperative dialysis predicted *overall mortality* in the multivariate analysis. CPB times and operation times were no independent predictors for overall mortality in this collective (Table 5).

In the patients collective excluding the *intraoperative deaths*, multivariate analysis revealed postoperative lactate levels, amylase levels, intraoperative need for thrombcyte concentrates and ECMO support to be predictors of mortality (Table 6).

Intraoperative death was predicted by CABG, absence of reliable ECMO support (before 2009) and intraoperative FFP usage.

Table 1: Patient's characteristics. Patients characteristics. Continuous variables are presented with the standard deviation; categoric variables are presented as number (%), CTEPH: chronic thromboembolic pulmonary hypertension.

Euroscore	14.92 ±15.35
Age (years)	59.29 ±13.3
Sex, male (n)	69.2% (166)
Re-operation % (n)	39.6% (95)
Endocarditis % (n)	10.9 (26)
Acute aortic dissection	25.4 (61)
CTEPH	3.8 (9)
Acute myocardial infarction	3.8 (9)
Tumor	1.3 (3)

Table 2: Operational details and early outcome. Operational details and early outcome. Continuous variables are presented with the standard deviation or range; categoric variables are presented as number. RBC: Red packed blood cells, FFP: Fresh frozen plasma, TC: thrombocyte concentrates, ECMO: extra-corporeal membrane oxygenation, IABP: intra-aortic balloon pump, ICU Intensive care unit.

CPB times (min)	356.53 ± 55.06
Operation times (min)	500.47 ± 96.56
Aortic clamp times (min)	166.18 ± 65.95
Euroscore	14.92 ± 15.35
Death intraoperative % (n)	11.7 (28)
Death intra-hospital % (n)	32.9 (79)
Cumulative mortality	50.4 (121)
Intraoperativly:	
RBC	13.77 ± 12.63
FFP	10.21 ± 8.38
TC	3.96 ± 3.37 (range: 0-30)
Overall:	
RBC	24.78 ± 21.57
FFP	20.78 ± 18.57
TC	10.03 ± 18.06
ECMO support % (n)	15.0 (36)
IABP support % (n)	19.2 (46)
Ventilation times (hours)	140.14 ± 269.81
ICU stay (days	11.32 ± 16.44
Hospital stay	22.09 ± 20.97 (range: 1-173)
Stroke % (n)	11.1 (24)
Postoperative dialysis % (n)	35.9 (78)
Re-Thoracotomy % (n)	30.4 (66)

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Establishment of reliable ECMO support may result in reduced intraoperative deaths. To further evaluate the impact of ECMO support on our patients collective, two groups were formed, Group 1 before establishment of a 24/7 availability of ECMO and Group 2 after the general availability of ECMO support, beginning after 2009. Between the years 1996 and 12/2008, 9 (14%) patients received ECMO support perioperativly, whereas after general availability after 2009, 22 patients (26.2%) (p<0.001) received ECMO support. The two groups were comparable in indications for surgery with a similar Euroscore (Table 7).

Intraoperative death was significantly reduced in group 2 (Group 1 17.9% vs. Group 2 2.4%, p<0.001). However cumulative in-hospital mortality remained the same (Group 1 49.4% vs. Group 2 52.4%, p=0.686).

Table 3: Operational procedures. Performed operational procedures, simplified to give an overview about the performed heterogeneous surgery. Categoric variables are presented as number, CABG: Coronay artery bypass grafting, FET: Frozen Elephant trunk technique, ET: "Classical" Elephant trunk technique, TAA: Throacoabdominal aortic aneurysm, PTE: Pulmonary Thromboendarterectomy, VSD: ventricular septum defect.

single valve repair/replacement	
w/o CABG	15
w CABG	14
double valve repair/replacement	
w/o CABG	15
w CABG	12
tripple valve repair/replacement	
w/o CABG	2
w CABG	3
Aortic surgery	
Ascending aortic replacment	
w/o CABG	5
w CABG	5
Ascending aortic replacment+ Aortic valve repair/replacement	
w/o CABG	15
w CABG	11
Ascending aortic/prox. arch replacment	
w/o CABG	2
w CABG	2
Ascending aortic/prox. arch replacment + Aortic valve repair/replacement	
w/o CABG	29
w CABG	20
Ascending aortic/complete arch replacment (FET/ET)	
w/o CABG	15
w CABG	9
Ascending aortic/complete arch replacment (FET/ET) + Aortic valve repair/ replacement	
w/o CABG	19
w CABG	5
CABG	15
TAA	10
PTE	9
Tumour	3
ROSS	5
VSD	1

Table 4: Univariate and multivariate analysis of risk factors for *intraoperative death.* RBC: Red packed blood cells, FFP: Fresh frozen plasma, ECMO: extra-corporeal membrane oxygenation, IABP: intra-aortic balloon pump, RBC: Red packed blood cells, FFP: Fresh frozen plasma, TC: thrombocyte concentrates.

Variable	Univariate	Multivariate		
	P	P	Exp (B)	95% confindence interval
Acute myocardial infarction	0.016			
Bental	0.102			
CABG	0.000	0.001	4.556	0.036-0.75
DOR	0.08			
ECMO availability	0.00	0.02	0.164	0.036-0.75
ECMO yes/no	0.037			
IABP yes/no	0.015			
Age	0.126			
Operation time	0.053			
CPB time	0.363			
Aortic clamp time	0.003			
RBC	0.00			
FFP	0.000	0.017	0.871	0.777-0.976
TC	0.318			
Euroscore	0.242			

Table 5: Univariate and multivariate analysis of risk factors for *overall death.* **ECMO**: extra-corporeal membrane oxygenation, CPB: cardiopulmonary bypass, RBC: Red packed blood cells, FFP: Fresh frozen plasma, TC: thrombocyte concentrates.

Variable	Univariate	Multivariate		
	P	P	Exp (B)	95% confindence interval
sex	0.007	0.015	0.427	0.215-0.848
endocarditis	0.005	0.001	6.350	2.093-19.266
triple valve surgery	0.010			
ascending aorta	0.092			
CABG	0.018	0.036	2.029	1.047-3.932
re-thoracotomy	0.010			
dialysis	0.000	0.00	5.381	2.690-10.765
ECMO yes/no	0.001			
age	0.001	0.032	1.029	1.002-1.056
Operation time	0.082			
CPB time	0.030			
Aortic clamp time	0.040	0.019	0.994	0.990-0.999
RBC	0.156			
FFP	0.687			
TC	0.030	0.03	1.1146	1.046-1.255
Euroscore	0.000			

Discussion

Prolonged CPB times are associated with an increase in

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mortality and morbidity [2]. Even in isolated aortic valve surgery and CPB times above 90 minutes excluded, CPB time remains a significant factor for blood loss, ICU and hospital length of stay as well as in-hospital mortality [3]. The patient's collective in this study was predominantly sick, with high rates of acute aortic dissections, endocarditis and re-operations. These patients often require long CPB times since intraoperative problems are often encountered. However, even patients with a predicted low Euroscore sometimes require long CPB times due to unexpected intraoperative complications. At CPB times above 300 minutes, the CPB time does not longer predict the overall outcome. The longest CPB time survived in our cohort was above 500 minutes. This indicates that CPB time should not hinder the cardiac surgeon to continue surgery, since these patients requiring such excessive CPB times still have a chance of survival. The introduction of the ECMO and general availability lead to a significant reduction in intraoperative mortality, however, it had no effect on overall in-hospital mortality. Venous arterial ECMO therapy enables support of unstable patients and critically ill patients in cardiogenic shock and allows temporary hemodynamic stabilization with improvement of end-organ function [4]. Most patients after long CPB times require hemodynamic stabilization as well as respiratory support due to oxygenatory failure; therefore a venous/venous ECMO is not the preferred option in these patients [5,6].

Table 6: Univariate and multivariate analysis of risk factors for *overall death*, excluding intraoperative death. RBC: Red packed blood cells, FFP: Fresh frozen plasma, ECMO: extra-corporeal membrane oxygenation, IABP: intra-aortic balloon pump, RBC: Red packed blood cells, FFP: Fresh frozen plasma, TC: thrombocyte concentrates, CPB: cardiopulmonary bypass.

Variable	Univariate	Multivariate		
	P	P	Exp (B)	95% confindence interval
Sex	0.005			
Endocarditis	0.010			
Rethoracotomy	0.000			
Dialysis	0.000			
ECMO yes/no	0.000	0.002	11.149	2.399-51.818
ECMO availability	0.086			
age	0.004			
Operation time	0.008			
CPB time	0.049			
RBC	0.019			
FFP				
TC	0.022	0.010	1.662	1.127-2.425
Euroscore	0.000			
CK-MB	0.001			
GOT	0.005			
GPT	0.037			
LDH	0.011			
Lactat	0.015	0.032	1.123	1.010-1.248
Amylase	0.000	0.036	1.003	1.006
Lipase	0.003			
CRP	0.014			

Table 7: Subgroup analysis for Patients operated with ECMO standby vs. no general availability of ECMO support. Subgroup analysis for Patients operated with ECMO standby vs. no general availability of ECMO support. Continuous variables are presented with the standard deviation; categoric variables are presented as number (%). RBC: Red packed blood cells, FFP: Fresh frozen plasma, TC: thrombocyte concentrates, ECMO: extra-corporeal membrane oxygenation, IABP: intra-aortic balloon pump, ICU: Intensive care unit.

	Group 1: Before 2009	Group 2: After 2009	P
Pre-operative data			
sex	69.9 (106)	67.9 (57)	p=0.771
Age (years)	58.41±13.37	60.32 ± 13.17	p=0.381
Re-operation % (n)	39.1 (61)	40.5 (34)	p=0.89
Endocarditis % (n)	9 (14)	14.3 (12)	p=0.276
Acute aortic dissection	26.3 (41)	23.8 (20)	p=0.757
CTEPH	3.8 (6)	3.6 (3)	p=0.29
Acute myocardial infarction	5.8 (9)	1.2 (1)	p=1
Tumor	1.3 (2)	1.2 (1)	p=1
Euroscore	16.26(69-79.48)	12.48 (0.64-76.73)	p=0.145
Intraoperative data			
CPB times (min)	358.18 ± 56.35	353.46 ± 52.774	p=0.528
Operation times (min)	497.13 ± 99.58	506.67 ± 90.93	p=0.557
Aortic clamp times (min)	160.1 ± 66.121	176.95 ± 64.62	p=0.059
ECMO % (n)	**9 (14)**	**26.2 (22)**	**p<0.001**
IABP % (n)	23.1 (36)	11.9 (10)	p=0.04
Intraoperative			
RBC	14.75 ± 14.089	12.3 ± 9.378	p=0.157
FFP	10.7 ± 8.51	9.9 ± 7.99	p=0.487
TC	4.2 (0-30)	3.52 (0-10)	p=0.347
Overall:			
RBC	24.4 ± 21.74	25.49 ± 21.36	p=0.417
FFP	21.15 ± 18.97	20.07 ± 17.886	p=0.428
TC	10.72 ± 21.49	8.72 ± 8.39	p=0.417
Outcome			
Death intraoperative % (n)	17.9 (28)	2.4 (2)	<0.001
Death in-hospital % (n)	31.4 (49)	42 (50)	p=0.005
Cumulative mortality	49.4 (77)	52.4 (44)	p=0.686
Ventilation times (hours)	78.62 ± 250.38	205.23 ± 248.49	p=0.001
ICU stay (days)	9.61 ± 17.93	10.88 ± 17.63	p=0.555
Hospital stay	19.87 ± 22.08	20.25 ± 17.64	p=0.348

As expected, the patients with such complicated operations and therefore long CPB times are prone for complications [7,8]. The re-thoracotomy rate was above 30% (excluding patients with intraoperative death). Kidney function was affected in almost all patients with a high rate of requirement for dialysis postoperatively [9]. Euroscore failed to predict mortality in this group [6]. Nonetheless, the mortality in this patient collective well exceeded the predicted Euroscore due to a negative selection of only those patients with long CPB times. This might in fact be due to rather unexpected complications encountered such as the rare entity of iatrogenic aortic dissections and alike. CABG was an independent risk factor for intraoperative and overall death. This is most likely due to rescue attempts during cardiac

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surgery, performing CABG as a bailout if the weaning from CBP is unsuccessful and myocardial ischemia has to be expected.

Re-sternotomy is usually due to technical issues regarding the operation or coagulopathy. In our study, longer CPB times were associated with an increased need for blood transfusions. This underlines the hypothesis, that the longer CPB times, the longer contact between foreign surfaces of the extracorporeal circuit resulting in increased severity of systemic inflammatory response. However, CRP as a marker for systemic inflammation was not increased with longer CPB times [10].

Longer cross clamp times are associated with a great risk of myocardial ischemia [2]. However, in our long CPB times, we were not able to identify CPB or cross clamp time as a significant factor determining creatinine kinase muscle-brain isoenzyme (CK-MB), creatinine kinase (CK) or myoglobine release a surrogate marker for myocardial ischemia (p=0.573 CK-MB, p=0.112 CK, p=0.626 myoglobine). Perioperative myocardial infarction remains frequent in cardiac surgery with an incidence from 8% to 35% [11]. This wide variation is due to criteria and tests employed by different investigators institutions. However, the pathogene1perioperative myocardial infarction is not well understood. Inadequate myocardial protection during cardiopulmonary bypass (CPB), perioperative vasospasm, and atheroembolism are some of the current theories [12,13]. Increased duration of CPB and aortic occlusion are associated with a higher incidence of myocardial infarction [2].

As expected there were several early and independent markers to predict postoperative death. These were all markers of kidney and liver function such as lactate levels, amylase. Therefore, one can conclude that the damage to the organs is done already intraoperativly affecting the overall survival in our group.

Conclusion

Every cardiac surgery can possibly go wrong, even if the Euroscore predicts a low morbidity and mortality. If intraoperative encountered problems occur and long CPB times are needed to handle them, even very long CPB times can be survived, however the mortality and morbidity is high. The introduction of ECMO support had a great impact on intraoperative mortality, however the overall mortality seems to be unaffected by ECMO support in this collective.

Limitations

Limitations to this study is the retrospective data evaluation, the lack of a control group and the long time course over which operational techniques and CBP support have changed significantly. However, a long term follow up would be possibly biased by the very heterogenous patient collective. We assume that within a longer time frame, the underlying disease of the patients would make a comparison of mid to long term survival very difficult.

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