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Cross-clamp time is an independent predictor of mortality and morbidity in low- and high-risk cardiac patients

Nael Al-Sarraf[a,b,*], Lukman Thalib[c], Anne Hughes[a], Maighread Houlihan[a], Michael Tolan[a], Vincent Young[a], Eillish McGovern[a]

[a] Department of Cardiothoracic Surgery, St. James's Hospital, Dublin 8, Ireland
[b] Department of Cardiothoracic Surgery, Chest Disease Hospital, Kuwait city, Kuwait
[c] Department of Community Medicine (Biostatistics), Faculty of Medicine, Kuwait University, Kuwait

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ABSTRACT

Objectives: We sought to assess the effects of aortic cross-clamp time (XCL) on outcome following cardiac surgery in low- and high-risk patients.
Methods: This is a retrospective review of prospectively collected departmental data of all patients who underwent cardiac surgery over 8-year period. Our cohort consisted of 3799 consecutive patients sub-divided into low-risk (Euro SCORE < 6, $n = 2691$, 71%) and high-risk (Euro SCORE ≥ 6, $n = 1108$, 29%). Each class was further stratified into three groups based on their corresponding XCL time. Group 1 (XCL $\leq$ 60 min), group 2 (XCL $>$ 60 but $\leq$ 90 min) and group 3 (XCL $>$90 min). Postoperative morbidity and in-hospital mortality were analysed.
Results: Univariate analysis showed the following to be significantly associated with increased XCL time in both low- and high-risk patients: low cardiac output, prolonged ventilation time, renal complications, prolonged hospital stay, blood transfusion and increased mortality ($p < 0.05$). By using multiple logistic regression, aortic XCL time $>$60 min was independent risk factor for low cardiac output, prolonged ventilation, renal complication, blood transfusion, mortality and prolonged hospital stay in both groups. By using XCL time as a continuous variable, an incremental increase of 1 min interval in XCL time was associated with a 2% increase in mortality in both groups.
Conclusion: Prolonged cross-clamp time significantly correlates with major post-operative morbidity and mortality in both low- and high-risk patients. This effect increases with increasing XCL time. Prior knowledge on this effect can help in preventing some of these complications.

1. Introduction

Historically, aortic cross-clamp (XCL) time was linked to adverse outcome following cardiac surgery.[1–3] However, whether or not XCL time has the same effect on low- vs. high-risk cardiac surgery patients remains unknown. In this study we have attempted to link the effect of XCL time to post-operative outcome in both low- and high-risk patients, thereby increasing our understanding of its potential implication in the cardiac surgery setting with the hope of potentially reducing its deleterious effect.

2. Patients and methods

2.1. Patients

This is a retrospective review of a prospectively collected departmental database (Patient Analysis and Tracking System, Dendrite Clinical, UK). All patients who underwent coronary artery bypass graft (CABG), isolated valve surgery (mitral, aortic, tricuspid or combination), or both in department of cardiothoracic surgery at St. James hospital between the period of February 2000 and July 2008 were reviewed. A total of 3799 consecutive patients were included in the study. All data were collected prospectively in a departmental database through the input of a dedicated database manager. Euro SCORE[4] was used to stratify patients into low-risk (i.e. Euro SCORE < 6) and high-risk (i.e. Euro SCORE ≥ 6) groups. Each of these two groups was analysed separately. Each of these two subsets was then stratified into 3 subgroups based on their aortic cross-clamp

* Corresponding author. Department of Cardiothoracic Surgery, Chest Disease Hospital, P.O. Box 718, Kuwait city 46308, Kuwait. Tel.: +965 66600543; fax: +965 4741504.
E-mail address: trinityq8@hotmail.com (N. Al-Sarraf).

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Table 1
Preoperative characteristics and their distribution among the various groups with Euro SCORE < 6 ($n = 2691$).

Variable	Time ≤ 60 min (control) ($n = 1510$)	Time > 60 to ≤90 min ($n = 859$)	Time > 90 min ($n = 322$)	*P*-value
Age (years)				
Mean ± SD	63.6 ± 9.5	64.5 ± 10.4	65.2 ± 11.6	0.015
Gender				
Female	344 (23%)	220 (26%)	91 (28%)	
Male	1166 (77%)	639 (74%)	231 (72%)	0.066
Angina (CCS) class				
0–2	623 (41%)	455 (53%)	213 (66%)	
3–4	887 (59%)	404 (47%)	109 (34%)	<0.001
NYHA score				
≤II	923 (61%)	465 (54%)	115 (36%)	
>II	587 (39%)	394 (46%)	207 (64%)	<0.001
Heart failure				
Yes	180 (12%)	186 (22%)	149 (46%)	
No	1330 (88%)	673 (78%)	173 (54%)	<0.001
Number of MI				
None	848 (56%)	548 (64%)	236 (73%)	
One	547 (36%)	254 (29%)	65 (20%)	
Two or more	115 (8%)	57 (7%)	21 (7%)	<0.001
Interval of MI to surgery				
None	848 (56%)	548 (64%)	236 (73%)	
<90 days	305 (20%)	150 (17%)	38 (12%)	
>90 days	357 (24%)	161 (19%)	48 (15%)	<0.001
Diabetes mellitus				
None	1223 (81%)	705 (82%)	270 (84%)	
Insulin dependent	60 (4%)	39 (5%)	6 (2%)	
Non-insulin dependent	227 (15%)	115 (13%)	46 (14%)	0.225
Hypercholesterolemia				
Yes	1117 (74%)	525 (61%)	164 (51%)	
No	393 (26%)	334 (39%)	158 (49%)	<0.001
Hypertension				
Yes	827 (55%)	450 (52%)	151 (47%)	
No	683 (45%)	409 (48%)	171 (53%)	0.033
Smoking status				
Current smokers	247 (16%)	120 (14%)	47 (15%)	
Former smokers	827 (55%)	437 (51%)	158 (49%)	
Non-smokers	436 (29%)	302 (35%)	117 (36%)	0.008
Chronic obstructive pulmonary disease				
Yes	135 (9%)	86 (10%)	40 (12%)	
No	1375 (91%)	773 (90%)	282 (88%)	0.148
Cerebrovascular accident				
Yes	108 (7%)	86 (10%)	34 (11%)	
No	1402 (93%)	773 (90%)	288 (89%)	0.020
Peripheral vascular disease				
Yes	277 (18%)	113 (13%)	40 (12%)	
No	1233 (82%)	746 (87%)	282 (88%)	0.001
Arrhythmia				
Yes	115 (8%)	128 (15%)	104 (32%)	
No	1395 (92%)	731 (85%)	218 (68%)	<0.001
Extra-cardiac arteriopathy				
Yes	97 (6%)	53 (6%)	18 (6%)	
No	1413 (94%)	806 (94%)	304 (94%)	0.849
Extent of coronary artery disease				
Normal	99 (6%)	245 (29%)	110 (34%)	
Single/double	372 (25%)	103 (12%)	97 (30%)	
Triple	1039 (69%)	511 (59%)	115 (36%)	<0.001
Left main stem disease				
Yes	420 (28%)	171 (20%)	41 (13%)	<0.001
No	1090 (72%)	688 (80%)	281 (87%)	
Ejection fraction				
<50%	543 (36%)	355 (41%)	153 (48%)	
≥50%	967 (64%)	504 (59%)	169 (52%)	<0.001
Intra-aortic balloon pump				
Yes	23 (2%)	7 (1%)	4 (1%)	
No	1487 (98%)	852 (99%)	318 (99%)	0.332
Priority				
Elective/urgent	1441 (95%)	837 (97%)	303 (94%)	
Emergency/salvage	69 (5%)	22 (3%)	19 (6%)	0.013
Cardiac procedure				
Isolated CABG	1393 (92%)	508 (59%)	41 (13%)	
CABG + valve	9 (1%)	91 (11%)	163 (50%)	
Isolated valve	108 (7%)	260 (30%)	118 (37%)	<0.001
Body mass index (kg/m^2)				
Mean ± SD	27.6 ± 4.6	27.6 ± 4.6	26.7 ± 4.3	0.006
Cardiopulmonary bypass time (minutes)				
Mean ± SD	84.7 ± 22.4	116.0 ± 23.4	156.4 ± 42.3	<0.001

CABG: Coronary artery bypass graft; CCS: Canadian cardiovascular society; NYHA: New York heart association; MI: Myocardial infarction; SD: Standard deviation.

(XCL) time as follows: group 1 is clamp time ≤60 min (control), group 2 is clamp time >60 min–≤90 min and group 3 is clamp time >90 min. Outcome measures studied included in-hospital mortality, post-operative complications, length of hospital stay and intensive care unit (ICU) stay. This study and the departmental database were both approved by our institutional review board. Individual patient consent was obtained for entry into the database. However, our institutional review board waived the need for individual patient consent for this study.

2.2. Cardiopulmonary bypass (CPB) and definitions

All cardiac surgeries were performed through a median sternotomy with CPB. Our CPB technique and myocardial protection have been previously reported.[5] Following full anticoagulation with heparin given at a dose of 300 IU/kg to maintain an activated clotting time of 400–600 s, CPB was instituted using ascending aortic cannulation and a two-stage right atrial venous cannulation. A roller pump (jostra HL 20) and hollow-fibre membrane oxygenator (Optima, Cobe Cardiovascular Inc.) were used. The extracorporeal circuit was primed with 1400 ml of Hartmann's solution and 5000 IU heparin. CPB was maintained with non-pulsatile flow with a minimum flow rate of 2.4 L/m^2/min at normothermia with temperature was allowed to drift to 32 °C. Arterial line filtration (Sentoy, Cobe Cardiovascular Inc.) was used in all the cases. Shed blood was recycled using cardiotomy suction. Acid-base was managed with alpha stat control. Myocardial protection was achieved with intermittent antegrade cold/tepid blood cardioplegia. On completion of all distal anastomoses, the aortic cross-clamp was removed and the proximal anastomoses performed with partial aortic clamping. Valvular surgeries were performed under single aortic cross-clamp. In CABG and valve surgeries, the cardioplegia is given in an antegrade fashion through the distal anastomotic grafts which were constructed first. Heparin was reversed with protamine at 1:1 ratio on weaning off cardiopulmonary bypass.[5] Operative priority was determined by cardiothoracic surgeons according to standard criteria as we have previously reported.[6] Definitions for in-hospital mortality and complications (i.e. renal, neurological, gastrointestinal, pulmonary, infective and arrhythmias) were previously reported in detail.[7,8] Additive Euro SCORE was used in the risk stratification of cardiac surgery patients.[4]

2.3. Data analysis

We used logistic regression models to assess the relationship between the early binary clinical outcomes including in-hospital mortality and post-operative complications with the aortic cross-clamp time. Crude odds ratios, 95% confidence intervals along with the related *P*-values were obtained using univariate logistic regression. Adjusted odds ratios (OR) were obtained using multivariate logistic models accounting for possible confounding. High-risk and low-risk patients were analysed separately. In addition, multiple logistic regression was used to examine the effect of

incremental increase in aortic cross-clamp time on mortality as a continuous variable using 1 min increments of XCL time. All data were entered and analysed using SPSS version 17 (SPSS Inc., USA). The *P*-values were considered statistically significant when less than 0.05.

3. Results

Our cohort ($n = 3799$) consisted of 936 (25%) females and 2863 (75%) males. Age ranged from 19 to 89 years old with a mean (±1 SD) of 63.9 (±10.1) years old. In-hospital mortality overall was 3.5% (133 patients). The cohort was subdivided into two subsets based on the Euro SCORE stratification of surgical risk. The first subset included low-risk patients with Euro SCORE < 6 ($n = 2691$, 71%) and the second subset included high-risk patients with Euro SCORE ≥ 6 ($n = 1108$, 29%). Both of these groups were then divided into three groups based on their XCL time as follows: clamp time ≤60 min (control group), clamp time >60 but ≤ 90 min, and clamp time >90 min. Results hereby are presented in a systemic order: Tables 1–4 are for patients with Euro SCORE < 6, and Tables 5–8 are results for patients with Euro SCORE ≥ 6. Preoperative factors and patients characteristics are summarized in Table 1 for patients with Euro SCORE < 6 and their corresponding post-operative complications is summarized in Table 2, with their relevant *p*-values as determined by univariate analysis. Crude odd ratios and adjusted odd ratios (OR) for early clinical outcomes of aortic cross-clamp time in patients with Euro SCORE < 6 using univariate and multiple logistic regression are summarized in Tables 3 and 4 respectively. The rate of most post-operative complications showed a significantly steady increase as the aortic XCL time increased with the exception of neurological complications and arrhythmias (Table 2). Similarly, the length of both hospital stay and intensive care unit (ICU) stay also showed a significantly steady increase with the incremental increase in aortic XCL time (Table 2). In addition, in-hospital mortality and blood transfusion requirements both showed similar association with aortic XCL time. By using multiple logistic regression, post-operative complications

Table 2
Univariate analysis of post-operative complications in the various groups with Euro SCORE < 6 ($n = 2691$).

Variable	Time ≤ 60 min (control) ($n = 1510$)	Time > 60 to ≤90 min ($n = 859$)	Time > 90 min ($n = 322$)	*P*-value
Low cardiac output				
Inotropes ± IABP	556 (37%)	389 (45%)	210 (65%)	
None	954 (63%)	470 (55%)	112 (35%)	<0.001
Arrhythmias				
Yes	747 (49%)	441 (51%)	170 (53%)	
No	763 (51%)	418 (49%)	152 (47%)	N/S
Re-operation				
Yes	68 (5%)	60 (7%)	37 (11%)	
No	1442 (95%)	799 (93%)	285 (89%)	<0.001
Ventilation time				
<24 h	1426 (94%)	790 (92%)	258 (80%)	
>24 h	84 (6%)	69 (8%)	64 (20%)	<0.001
Pulmonary complications				
Yes	220 (15%)	153 (18%)	82 (25%)	
No	1290 (85%)	706 (82%)	240 (75%)	<0.001
Neurological complications				
Yes	28 (2%)	30 (3%)	4 (1%)	
No	1482 (98%)	829 (97%)	318 (99%)	0.015
Infective complications				
Yes	106 (7%)	71 (8%)	43 (13%)	
No	1404 (93%)	788 (92%)	279 (87%)	0.001
Renal complications				
Yes	102 (7%)	80 (9%)	43 (13%)	
No	1408 (93%)	779 (91%)	279 (87%)	<0.001
Gastrointestinal complications				
Yes	21 (1%)	17 (2%)	19 (6%)	
No	1489 (99%)	842 (98%)	303 (94%)	<0.001
Readmission to ICU				
Yes	43 (3%)	39 (5%)	20 (6%)	
No	1467 (97%)	820 (95%)	302 (94%)	0.006
ICU stay (days)				
Mean ± SD	2.0 ± 4.0	3.2 ± 9.3	4.3 ± 8.3	<0.001
Post-op stay (days)				
Mean ± SD	8.2 ± 9.7	10.3 ± 14.8	12.9 ± 14.2	<0.001
Blood transfusion				
Yes	597 (40%)	424 (49%)	219 (68%)	
No	913 (60%)	435 (51%)	103 (32%)	<0.001
Status				
Alive	1474 (98%)	825 (96%)	297 (92%)	
Dead	36 (2%)	34 (4%)	25 (8%)	<0.001

IABP: Intra-aortic balloon pump; ICU: Intensive care unit; SD: standard deviation.

Table 3
Crude odds ratios for early clinical outcomes of aortic cross-clamp time in patients with Euro SCORE < 6 using multiple logistic regression ($n = 2691$).

Variable [a]	Time ≤ 60 min OR (95% CI)	Time > 60 ≤ 90 min OR (95% CI)	Time > 90 min OR (95% CI)
Post-op low cardiac output (Inotropes ± IABP)	1.0 (–)	1.4 (1.2–1.7)*	3.2 (2.5–4.1)*
Re-operation	1.0 (–)	1.6 (1.1–2.3)*	2.8 (1.8–4.2)*
Ventilation time (<24 vs. >24 h)	1.0 (–)	1.5 (1.1–2.1)*	4.2 (3.0–6.0)*
Post-op arrhythmias	1.0 (–)	1.1 (0.9–1.3)	1.1 (0.9–1.5)
Pulmonary complications	1.0 (–)	1.2 (1.0–1.6)*	2.0 (1.5–2.7)*
Infective complications	1.0 (–)	1.2 (0.9–1.6)	2.0 (1.4–3.0)*
Renal complications	1.0 (–)	1.4 (1.0–1.9)*	2.1 (1.5–3.1)*
Gastrointestinal complications	1.0 (–)	1.4 (0.8–2.7)	4.4 (2.4–8.4)*
Neurological complications	1.0 (–)	1.9 (1.1–3.2)	0.7 (0.2–1.9)
Readmission to ICU	1.0 (–)	1.6 (1.0–2.5)*	2.3 (1.3–3.9)*
ICU stay (days)	1.0 (–)	1.3 (1.1–1.6)*	3.0 (2.4–3.9)*
Post-op stay (days)	1.0 (–)	1.7 (1.5–2.1)*	3.5 (2.7–4.6)*
Blood transfusion	1.0 (–)	1.5 (1.3–1.8)*	3.3 (2.5–4.2)*
In-hospital mortality	1.0 (–)	1.7 (1.0–2.7)*	3.4 (2.0–5.8)*

CI: confidence interval; IABP: intra-aortic balloon pump; ICU: intensive care unit; OR: odds ratio.
[a] significant variables are highlighted with asterisk.

Table 4
Adjusted odds ratios (by age and gender) related to early clinical outcomes of aortic cross-clamp time in patients with Euro SCORE < 6 using multiple logistic regression ($n = 2691$).

Variable [a]	Time ≤ 60 min OR (95% CI)	Time > 60 ≤ 90 min OR (95% CI)	Time > 90 min OR (95% CI)
Post-op low cardiac output (Inotropes ± IABP)	1.0 (–)	1.4 (1.2–1.6)*	3.2 (2.4–4.1)*
Re-operation	1.0 (–)	1.6 (1.1–2.2)*	2.6 (1.7–4.0)*
Ventilation time (<24vs. >24 h)	1.0 (–)	1.4 (1.0–2.0)*	3.9 (2.7–5.6)*
Post-op arrhythmias	1.0 (–)	1.0 (0.9–1.2)	1.1 (0.8–1.4)
Pulmonary complications	1.0 (–)	1.2 (1.0–1.6)	1.9 (1.4–2.6)*
Infective complications	1.0 (–)	1.2 (0.9–1.6)	2.0 (1.4–2.9)*
Renal complications	1.0 (–)	1.3 (1.0–1.8)	1.9 (1.3–2.7)*
Gastrointestinal complications	1.0 (–)	1.4 (0.7–2.6)	4.0 (2.1–7.6)*
Neurological complications	1.0 (–)	1.8 (1.1–3.1)	0.6 (0.2–1.7)
Readmission to ICU	1.0 (–)	1.6 (1.0–2.5)*	2.2 (1.2–3.7)*
ICU stay (days)	1.0 (–)	1.3 (1.1–1.6)*	2.9 (2.3–3.7)*
Post-op stay (days)	1.0 (–)	1.7 (1.4–2.0)*	3.5 (2.7–4.6)*
Blood transfusion	1.0 (–)	1.4 (1.2–1.7)*	3.3 (2.5–4.3)*
In-hospital mortality	1.0 (–)	1.6 (1.0–2.6)*	3.1 (1.8–5.3)*

CI: confidence interval; IABP: intra-aortic balloon pump; ICU: intensive care unit; OR: odds ratio.
[a] Significant variables are highlighted with asterisk.

Table 5
Preoperative characteristics and their distribution among the various groups with Euro SCORE ≥ 6 ($n = 1108$).

Variable	Time ≤ 60 min (control) ($n = 618$)	Time > 60 to ≤90 min ($n = 362$)	Time > 90 min ($n = 128$)	*P*-value
Age (years)				
Mean ± SD	63.4 ± 9.3	63.8 ± 11.3	64.9 ± 11.7	0.311
Gender				
Female	165 (27%)	80 (22%)	36 (28%)	
Male	453 (73%)	282 (78%)	92 (72%)	0.209
Angina (CCS) class				
0–2	272 (44%)	190 (52%)	85 (66%)	
3–4	346 (56%)	172 (48%)	43 (34%)	<0.001
NYHA score				
≤II	385 (62%)	202 (56%)	47 (37%)	
>II	233 (38%)	160 (44%)	81 (63%)	<0.001
Heart failure				
Yes	68 (11%)	65 (18%)	55 (43%)	
No	550 (89%)	297 (82%)	73 (57%)	<0.001
Number of MI				
None	344 (56%)	242 (67%)	100 (78%)	
One	237 (38%)	90 (25%)	25 (20%)	
Two or more	37 (6%)	30 (8%)	3 (2%)	<0.001
Interval of MI to surgery				
None	344 (56%)	242 (67%)	100 (78%)	
<90 days	126 (20%)	44 (12%)	13 (10%)	
>90 days	148 (24%)	76 (21%)	15 (12%)	<0.001
Diabetes mellitus				
None	503 (81%)	309 (85%)	107 (84%)	
Insulin dependent	25 (4%)	11 (3%)	4 (3%)	
Non-insulin dependent	90 (15%)	42 (12%)	17 (13%)	0.615
Hypercholesterolemia				
Yes	477 (77%)	216 (60%)	65 (51%)	
No	141 (23%)	146 (40%)	63 (49%)	<0.001
Hypertension				
Yes	364 (59%)	207 (57%)	58 (45%)	
No	254 (41%)	155 (43%)	70 (55%)	0.018
Smoking status				
Current smokers	88 (14%)	54 (15%)	16 (12%)	
Former smokers	340 (55%)	199 (55%)	65 (51%)	
Non-smokers	190 (31%)	109 (30%)	47 (37%)	0.702
Chronic obstructive pulmonary disease				
Yes	48 (8%)	34 (9%)	21 (16%)	
No	570 (92%)	328 (91%)	107 (84%)	0.009
Cerebrovascular accident				
Yes	47 (8%)	25 (7%)	10 (8%)	
No	571 (92%)	337 (93%)	118 (92%)	0.905
Peripheral vascular disease				
Yes	107 (17%)	45 (12%)	24 (19%)	
No	511 (83%)	317 (88%)	104 (81%)	0.084
Arrhythmia				
Yes	46 (7%)	56 (15%)	41 (32%)	
No	572 (93%)	306 (85%)	87 (68%)	<0.001
Extra-cardiac arteriopathy				
Yes	35 (6%)	27 (7%)	8 (6%)	
No	583 (94%)	335 (93%)	120 (94%)	0.537
Extent of coronary artery disease				
Normal	36 (6%)	92 (26%)	44 (34%)	
Single/double	172 (28%)	48 (13%)	39 (31%)	
Triple	410 (66%)	222 (61%)	45 (35%)	<0.001
Left main stem disease				
Yes	189 (31%)	72 (20%)	14 (11%)	
No	429 (69%)	290 (80%)	114 (89%)	<0.001
Ejection fraction				
<50%	207 (33%)	134 (37%)	54 (42%)	
≥50%	411 (67%)	228 (63%)	74 (58%)	0.140
Intra-aortic balloon pump				
Yes	4 (1%)	5 (1%)	2 (2%)	
No	614 (99%)	357 (99%)	126 (98%)	0.421
Priority				
Elective/urgent	602 (97%)	350 (97%)	123 (96%)	
Emergency/salvage	16 (3%)	12 (3%)	5 (4%)	0.655
Cardiac procedure				
Isolated CABG	570 (92%)	217 (60%)	19 (15%)	
CABG + valve	3 (1%)	47 (13%)	62 (48%)	
Isolated valve	45 (7%)	98 (27%)	47 (37%)	<0.001
Body mass index (kg/m^2)				
Mean ± SD	28.1 ± 5.8	27.6 ± 4.6	27.6 ± 4.7	0.298
Cardiopulmonary bypass time (min)				
Mean ± SD	84.3 ± 22.6	116.9 ± 23.8	157.1 ± 42.9	<0.001

(*continued on next page*)

Table 5 (*continued*)

CABG: Coronary artery bypass graft; CCS: Canadian cardiovascular society; MI: Myocardial infarction; NYHA: New York heart association; SD: Standard deviation.

that were significantly associated with prolonged aortic XCL time were: low cardiac output, re-operation, prolonged ventilation, pulmonary, infective, renal and gastrointestinal complications. Similarly, the rate of ICU readmission together with both hospital and ICU stay were significantly associated with prolonged XCL time. In-hospital mortality rate was highest in patients with XCL time >90 min (OR 3.1) and intermediate in XCL time >60 min ≤ 90 min (OR 1.6) relative to the control group (XCL time <60 min). Blood transfusion requirement (Table 4) were also significantly increased in patients with prolonged XCL time (OR 3.3 for XCL > 90 min, and OR 1.4 for XCL > 60 ≤ 90 min).

Table 6
Univariate analysis of post-operative complications in the various groups with Euro SCORE ≥ 6 ($n = 1108$).

Variable	Time ≤ 60 min (control) ($n = 618$)	Time > 60 to ≤90 min ($n = 362$)	Time > 90 min ($n = 128$)	*P*-value
Post-op low cardiac output				
Inotropes ± IABP	217 (35%)	137 (38%)	80 (63%)	
None	401 (65%)	225 (62%)	48 (37%)	<0.001
Arrhythmias				
Yes	308 (50%)	179 (49%)	58 (45%)	
No	310 (50%)	183 (51%)	70 (55%)	0.643
Re-operation				
Yes	35 (6%)	22 (6%)	5 (4%)	
No	583 (94%)	340 (94%)	123 (96%)	0.652
Ventilation time				
<24 h	591 (96%)	339 (94%)	109 (85%)	
>24 h	27 (4%)	23 (6%)	19 (15%)	<0.001
Pulmonary complications				
Yes	93 (15%)	61 (17%)	28 (22%)	
No	525 (85%)	301 (83%)	100 (78%)	0.160
Neurological complications				
Yes	15 (2%)	8 (2%)	6 (5%)	
No	603 (98%)	354 (98%)	122 (95%)	0.290
Infective complications				
Yes	47 (8%)	38 (10%)	16 (12%)	
No	571 (92%)	324 (90%)	112 (88%)	0.116
Renal complications				
Yes	35 (6%)	33 (9%)	16 (12%)	
No	583 (94%)	329 (91%)	112 (88%)	0.012
Gastrointestinal complications				
Yes	9 (1%)	10 (3%)	4 (3%)	
No	609 (99%)	352 (97%)	124 (97%)	0.259
Readmission to ICU				
Yes	22 (4%)	10 (3%)	5 (4%)	
No	596 (96%)	352 (97%)	123 (96%)	0.743
ICU stay (days)				
Mean ± SD	1.9 ± 3.6	2.5 ± 5.8	3.5 ± 9.8	0.008
Post-op stay (days)				
Mean ± SD	7.8 ± 6.7	8.7 ± 9.5	13.6 ± 20.3	<0.001
Blood transfusion				
Yes	271 (44%)	169 (47%)	89 (70%)	
No	347 (56%)	193 (53%)	39 (30%)	<0.001
Status				
Alive	608 (98%)	344 (95%)	118 (92%)	
Dead	10 (2%)	18 (5%)	10 (8%)	<0.001

IABP: Intra-aortic balloon pump; ICU: Intensive care unit; SD: standard deviation.

Table 7
Crude odds ratios for early clinical outcomes of aortic cross-clamp time in patients with Euro SCORE ≥ 6 using multiple logistic regression ($n = 1108$).

Variable	Time ≤ 60 min OR (95% CI)	Time > 60 ≤ 90 min OR (95% CI)	Time > 90 min OR (95% CI)
Post-op low cardiac output (Inotropes ± IABP)	1.0 (–)	1.1 (0.9–1.5)	3.1 (2.1–4.6)*
Post-op arrhythmias	1.0 (–)	1.0 (0.8–1.3)	0.8 (0.6–1.2)
Re-operation	1.0 (–)	1.1 (0.6–1.9)	0.7 (0.3–1.8)
Ventilation time (<24 vs. >24 h)	1.0 (–)	1.5 (0.8–2.6)	3.8 (2.1–7.1)*
Pulmonary complications	1.0 (–)	1.1 (0.8–1.6)	1.6 (1.0–2.5)
Neurological complications	1.0 (–)	0.9 (0.4–2.2)	2.0 (0.8–5.2)
Infective complications	1.0 (–)	1.4 (0.9–2.2)	1.7 (1.0–3.2)
Renal complications	1.0 (–)	1.7 (1.0–2.7)*	2.4 (1.3–4.4)*
Gastrointestinal complications	1.0 (–)	1.9 (0.8–4.8)	2.2 (0.7–7.2)
Re-admission to ICU	1.0 (–)	0.8 (0.4–1.6)	1.1 (0.4–3.0)
Intensive care stay (days)	1.0 (–)	1.2 (0.9–1.5)	2.3 (1.6–3.5)*
Hospital stay (days)	1.0 (–)	1.3 (1.0–1.6)	3.0 (2.0–4.6)*
Blood transfusion	1.0 (–)	1.1 (0.9–1.5)	2.9 (1.9–4.4)*
In-hospital mortality	1.0 (–)	3.2 (1.5–7.0)*	5.2 (2.1–12.7)*

Significant variables are highlighted with asterisk.
IABP: Intra-aortic balloon pump; CI: confidence interval; OR: odd ratio.

The results of analysis of high-risk patients (i.e. Euro SCORE ≥ 6) are shown in Tables 5–8. Preoperative factors and patients characteristics are summarized in Table 5 with their relevant *p*-values as determined by univariate analysis while Table 6 is a summary of the univariate analysis of post-operative complications in this group. As shown in Table 6, the rate of following post-operative complications was significantly increased with increasing aortic XCL time: low cardiac output, prolonged ventilation time, renal complications, ICU and hospital stay. All of these have shown a steady incremental increase in relation to the incremental increase in aortic XCL time. Furthermore, the blood transfusion requirements and in-hospital mortality also showed a significant correlation with the increase in aortic XCL time. Crude odd ratios and adjusted odd ratios for early clinical outcomes of aortic cross-clamp time in patients with Euro SCORE ≥ 6 using univariate and multiple logistic regression are summarized in Tables 7 and 8 respectively. As shown in these tables, low cardiac output, prolonged ventilation time, renal complications, hospital and intensive care unit stays and blood transfusion requirements were all significantly increased as the aortic XCL time is increased. Similarly, mortality for high-risk patients with prolonged aortic XCL time >90 min were significantly higher (OR 4.7) than those with XCL time >60 ≤ 90 min (OR 3.1).

Table 8
Adjusted odds ratios (by age and gender) related to early clinical outcomes of aortic cross-clamp time in patients with Euro SCORE ≥ 6 using multiple logistic regression ($n = 1108$).

Variable [a]	Time ≤ 60 min OR (95% CI)	Time > 60 ≤ 90 min OR (95% CI)	Time > 90 min OR (95% CI)
Post-op low cardiac output (inotropes ± IABP)	1.0 (–)	1.1 (0.8–1.5)	3.0 (2.0–4.5)*
Arrhythmias	1.0 (–)	1.0 (0.7–1.2)	0.7 (0.5–1.1)
Re-operation	1.0 (–)	1.1 (0.6–1.8)	0.6 (0.2–1.7)
Ventilation time (<24 vs. >24 h)	1.0 (–)	1.5 (0.8–2.6)	3.8 (2.0–7.0)*
Pulmonary complications	1.0 (–)	1.1 (0.8–1.6)	1.5 (1.0–2.5)
Neurological complications	1.0 (–)	0.9 (0.4–2.1)	1.8 (0.7–4.8)
Infective complications	1.0 (–)	1.4 (0.9–2.2)	1.7 (0.9–3.1)
Renal complications	1.0 (–)	1.6 (1.0–2.6)	2.2 (1.2–4.2)*
Gastrointestinal complications	1.0 (–)	1.7 (0.7–4.4)	1.9 (0.6–6.3)
Intensive care stay (days)	1.0 (–)	1.3 (1.0–1.6)	3.0 (2.0–4.6)*
Readmission to ICU	1.0 (–)	0.8 (0.4–1.6)	1.0 (0.4–2.8)
Hospital stay (days)	1.0 (–)	1.2 (0.9–1.5)	2.3 (1.6–3.4)*
Blood transfusion	1.0 (–)	1.1 (0.9–1.5)	3.0 (1.9–4.5)*
In-hospital mortality	1.0 (–)	3.1 (1.4–6.8)*	4.7 (1.9–11.7)*

IABP: Intra-aortic balloon pump; CI: confidence interval; OR: odds ratio.
[a] Significant variables are highlighted with asterisk.

Table 9
Multiple logistic regression analysis showing the effect of aortic cross-clamp time as a continuous variable on in-hospital mortality using 1 min increments of XCL time in both groups.

Aortic cross-clamp time	In-hospital mortality	
	Euro SCORE < 6	Euro SCORE ≥ 6
Mortality (*n*/*N*)	95/2691	38/1108
Odds ratio	1.02	1.02
95% Confidence interval	1.01–1.03	1.01–1.03
P-value	<0.001	<0.001

n: number of patients with observed outcome; *N*: total number of sample.

A separate multiple logistic regression examining the effect of 1 min incremental increase in aortic cross-clamp time (as a continuous variable) on the risk of mortality in both groups is summarized in Table 9. As shown in this table, for every 1 min increase in XCL time, the odds of mortality increases by 2% (OR 1.02) [95% CI 1.01–1.03 *P*-value <0.001]. This was observed for both groups.

4. Discussion

Previous studies have highlighted increased risk of death and some complications in patients who are subjected to prolonged aortic cross-clamp time.[1–3] However, no data are available on the effect of aortic XCL time in both low- and high-risk cardiac surgery patients. In addition, the full spectrum of complications as a function of prolonged aortic cross-clamp time has not been reported in great detail. In this paper we sought to assess the relation between prolonged aortic XCL time and outcome in both low- and high-risk patients. By doing so, our understanding of the clinical significance of such clamp time will be strengthened leading to a better potential preventative strategies that can improve the clinical outcome.

As speculated, we found that prolonged aortic XCL time significantly correlated with worse clinical outcomes in both low-risk and high-risk cardiac surgery patients. The spectrum of complications included in-hospital mortality, prolonged hospitalization, prolonged ventilation, low cardiac output, higher requirements for blood transfusion and renal complications (Tables 4 and 8). This effect was similar in both low- and high-risk groups. Few previous studies have examined predictors of in-hospital mortality and among these, prolonged aortic XCL time was found to be significant.[1,2,9] However, all previous data were either presented as mean value of XCL time[2] or various differing cut-off values.[1,9] Doenst et al. have shown that prolonged XCL time was significant predictor of mortality in patients with ejection fraction >40%, but no correlation was shown with those with ejection fraction <40%.[1] The authors speculated that this lack of correlation was mainly due to high mortality seen in their series in patients with EF <40% at very short XCL times (<30 min). Our findings fit to some degree with those reported by Doenst et al., in that prolonged XCL time are associated with mortality in a linear fashion. However, in their work the mortality for patients with depressed ejection fraction (<40%), they observed a U-shaped curve with highest mortality seen in both ends of XCL time (i.e. <30 min and >90 < 120 min). A limitation to their work is that they did not stratify their cases on the basis of any risk scoring system as we have done, which might have potentially altered the results especially among the depressed ejection fraction group. Stratifying patients on the mere basis of their preoperative ejection fraction is not a true representative way of describing the mortality risk. In addition, some of these studies have also excluded patients with prolonged ischemic time[1] and no study so far have

uniformly stratified patients according to a scoring system to test the overall effect, as we have done.

Few potential reasons can explain the observed association between in-hospital mortality and prolonged aortic XCL time. Firstly, the range of post-operative complications observed in both groups of low- and high-risk patients in our study as a result of prolonged aortic XCL time were wide and included blood transfusion requirements, low cardiac output, prolonged ventilation, renal complications and prolonged hospital and ICU stay (Tables 4 and 8). In addition, low-risk groups with prolonged aortic XCL time had also higher rates of infective complications, pulmonary complications and gastrointestinal complications (Table 4). All of these complications can arise as a result of prolonged ischemia time and can directly affect post-operative mortality. For example, blood transfusion has been signalled previously to be as a significant occurring in cardiac surgery patients with prolonged aortic XCL time[3] and was reported to be associated with worse outcome following cardiac surgery.[10] In addition, renal failure post-cardiac surgery is also independently associated with mortality as we have previously shown among others.[5,11] Secondly, aortic XCL time is considered to reflect ischemic injury and despite better myocardial protection techniques used in the current era, it is still noted to affect mortality.[1] This is clearly shown in Table 9, where 1 min incremental increase in aortic cross-clamp time is associated with 2% increase in mortality (OR 1.02) in both groups. Thirdly, in the past, authors have shown that there is an increase in the catecholamine release as measured by epinephrine and norepinephrine levels during XCL of aorta.[12] This effect could be amplified by prolonged XCL time and as such we would expect a more pronounced effect of this sympathetic activation. Unfortunately, no study so far has elicited the mechanism by which aortic cross-clamp can produce its effects and such studies are desperately needed to understand more about the pathophysiological mechanisms underlying these effects.

There was no association between prolonged aortic cross-clamp time and arrhythmias and neurological complications following cardiac surgery. Arrhythmias are the result of hyper adrenergic stimulation that occurs following the stress of cardiac surgery and the use of inotropic medications post-surgery rather than ischemic time. Previous studies examining predictors of post-operative arrhythmias have shown lack of association between ischemic time and arrhythmias.[13,14] Neurological complications are the result of multiple preoperative and intraoperative factors such as advanced age, peripheral vascular disease, diabetes, aortic calcifications and intraoperative hypoperfusion rather than prolonged ischemic time.[15,16] The main hypothesis of neurological complications is direct embolization of unstable aortic plaques following aortic clamping rather than aortic cross-clamp time itself.

5. Limitation of the study

There are few limitations in our study. Firstly, our study remains a retrospective study despite the fact that all data were prospectively collected, and as such we can only report an association rather than causality. Secondly, some preoperative characteristics that were significantly different among the three groups could have contributed to the observed outcome. However, we relied on Euro SCORE for stratifying patients into low- and high-risk groups, thereby potentially limiting such an association to affect the observed outcome. Euro SCORE has one of the highest sensitivities and specificities among most cardiac surgery risk scoring systems.[17] However, within these acceptable limitations, we believe our work will shed more light into the subject and perhaps stimulate more research on this topic.

6. Conclusion

Prolonged aortic cross-clamp time significantly correlates with major post-operative morbidity and mortality in both low- and high-risk cardiac surgery patients. This effect increases with increasing XCL time. Prior knowledge on this effect can help in preventing some of these complications or reducing their incidence. Studies aimed at elucidating the mechanisms of these deleterious effects at cellular level are warranted.

Conflict of interest
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