Risk Factors of Postcardiotomy Ventricular Dysfunction in Moderate-to-high Risk Patients Undergoing Open-heart Surgery

Abstract

Introduction: Ventricular dysfunction requiring inotropic support frequently occurs after cardiac surgery, and the associated low cardiac output syndrome largely contributes to postoperative death. We aimed to study the incidence and potential risk factors of postcardiotomy ventricular dysfunction (PCVD) in moderate-to-high risk patients scheduled for open-heart surgery. **Methods:** Over a 5-year period, we prospectively enrolled 295 consecutive patients undergoing valve replacement for severe aortic stenosis or coronary artery bypass surgery who presented with Bernstein-Parsonnet scores >7. The primary outcome was the occurrence of PCVD as defined by the need for sustained inotropic drug support and by transesophageal echography. The secondary outcomes included in-hospital mortality and the incidence of any major adverse events as well as Intensive Care Unit (ICU) and hospital length of stay. **Results:** The incidence of PCVD was 28.4%. Patients with PCVD experienced higher in-hospital mortality (12.6% vs. 0.6% in patients without PCVD) with a higher incidence of cardiopulmonary and renal complications as well as a prolonged stay in ICU (median + 2 days). Myocardial infarct occurred more frequently in patients with PCVD than in those without PCVD (19 [30.2%] vs. 12 [7.6%]). By logistic regression analysis, we identified four independent predictors of PCVD: left ventricular ejection fraction <40% (odds ratio [OR] = 6.36; 95% confidence interval [CI], 2.59–15.60), age older than 75 years (OR = 3.35; 95% CI, 1.64–6.81), prolonged aortic clamping time (OR = 3.72; 95% CI, 1.66–8.36), and perioperative bleeding (OR = 2.33; 95% CI, 1.01–5.41). The infusion of glucose-insulin-potassium was associated with lower risk of PCVD (OR = 0.14; 95% CI, 0.06–0.33). **Conclusions:** This cohort study indicates that age, preoperative ventricular function, myocardial ischemic time, and perioperative bleeding are predictors of PCVD which is associated with poor clinical outcome.

Keywords: *Cardiopulmonary bypass, low cardiac output, myocardial ischemia, ventricular dysfunction*

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Introduction

Low cardiac output syndrome (LCOS) remains a dreadful complication occurring in 5%–15% of patients undergoing open-heart surgery.[1-4] Systemic hypoperfusion results in multiple organ dysfunction causing prolonged stay in the Intensive Care Unit (ICU) and significant postoperative morbidity and mortality.[5] Predictors of LCOS have been identified in large cohort studies such as advanced age, impaired systolic and diastolic ventricular function, recent myocardial infarct, renal failure, as well as emergent procedures and prolonged bypass or aortic cross-clamping times.[6,7]

Nowadays, transesophageal echocardiographic examination (TEE) has been widely adopted in cardiac surgery, and it has largely replaced the pulmonary artery catheter in evaluating cardiac function and in guiding cardiovascular treatments based on a more rational physiological approach.[8,9] Instead of measuring cardiac output by thermodilution, TEE coupled with standard hemodynamic monitoring provides the unique opportunity to properly diagnose and treat hypovolemia, vasoplegic syndrome, ischemia-related dyskinesia, and myocardial stunning at the bedside.[10] The term "postcardiotomy ventricular dysfunction" (PCVD) has been coined to define new onset or worsening heart failure that requires the administration of inotropes and/or mechanical support during the weaning period from the cardiopulmonary bypass (CPB).[4] Causes of PCVD are multifactorial, including surgical tissue trauma, myocardial ischemia-reperfusion injuries, downregulation of beta-adrenergic

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receptors, coronary embolization (e.g., air, atheroma particle), and activation of inflammatory and coagulation.[11] The incidence of PCVDs varies from 20% to 60% depending on the definition criteria and the case mix in cardiac surgical patients.[12,13] Although PCVD can be self-limited – resolving with transient pharmacological support – it may also herald a LCOS with its negative prognostic clinical implications.[4]

Given its high incidence, identification of patient- and procedure-related risk factors of PCVD may represent important targets for improving morbidity and mortality following cardiac surgery. The purpose of the current study was to examine modifiable and nonmodifiable risk factors of PCVD in a cohort of moderate-to-high risk patients undergoing aortic valve replacement (AVR) and/or coronary artery bypass surgery (CABG). This prospective cohort included all patients who were enrolled in a previous randomized control trial that was designed to evaluate the safety and cardioprotective effects of the infusion of glucose-insulin-potassium (GIK) before bypass.

Methods

Patient selection and study design

The cohort included patients with severe aortic valve stenosis and/or coronary artery disease who were scheduled for elective AVR and/or CABG at the University Hospital of Geneva. Eligible patients had a Bernstein-Parsonnet score higher than 7. Exclusion criteria consisted of emergent or off-pump surgery, preoperative critical condition, poorly controlled diabetes mellitus, severe liver disease (Child-Pugh C), and dementia or significant cerebrovascular disease.

This single-center trial was approved by the Institutional Review Board at the University Hospital of Geneva (CER: 08-095), it was registered on ClinicalTrials.gov (NCT00788242), and written consent was obtained from each eligible participant.

Prospective data were collected according to the checklist of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Perioperative management

The usual medications were continued up to the morning of the procedure, except diuretics, antiplatelets, and angiotensin-converting enzyme inhibitors or angiotensin II antagonists that were interrupted 1 day before. In the operating theater, all patients were equipped with an invasive arterial catheter, a central venous line and a bispectral monitor (BIS) of the electroencephalogram (Aspect Medical Systems A-2000 XP). Anesthesia management consisted of intrathecal morphine (10 mcg/kg), low doses of intravenous sufentanil and an infusion of propofol to target BIS values between 40 and 60. Cardiac preconditioning was also provided with volatile anesthetics (before CPB).

A TEE probe (Matrix Array Probe X7-2t; Philips Medical Systems, Andover, MA, USA) was introduced after anesthesia induction, and images were digitally acquired before and after CPB and stored with the iE33 ultrasound imaging system (Philips Medical Systems, Andover, MA, USA).[14] Patients were given either the GIK solution (human Actrapid, Novo Nordisk 20 IU and potassium chloride 10 mEq in 50 ml of 40% glucose) or a similar volume of normal saline over 40 min starting after the anesthetic induction.

After full heparinization, normothermic CPB was instituted with a nonpulsatile flow (2.2–2.5 L/min/m²) and alpha-stat control for acid–base management. The circuit and the membrane oxygenator were primed with 2 L of clear fluids (1 L Ringer-Acetate and 1 L of hydroxyethyl starch 6% 130/0.4). Mean arterial pressure (MAP) was maintained between 50 and 70 mmHg with vasoactive medications as necessary. During aortic cross-clamping, myocardial protection was achieved by intermittent antegrade infusion of cold blood. Antifibrinolytic therapy with tranexamic acid was administered before CPB (15 mg/kg intravenous over 10 min) and in the CPB priming fluid (10 mg/kg). Packed red blood cells were transfused if a hemoglobin level <60–65 g/L during CPB or <80–90 g/L after CPB was achieved; higher transfusion threshold was set in specific groups of patients (e.g., cerebrovascular disease, renal dysfunction, or marginal coronary vascularization).

At the end of the procedure, weaning from CPB was guided by TEE assessment and hemodynamic measurements. After de-airing the cardiac cavities and resumption of mechanical ventilation, the pump flow was gradually reduced and the heart was progressively filled. In addition to fluid loading, electrical atrioventricular pacing, vasopressors, and/or inotropes drugs were given to target the following hemodynamic endpoints: left ventricular (LV) end-diastolic diameter between 2.2 and 2.8 cm/m², MAP between 65 and 100 mmHg, and heart rate between 70 and 100 beats/min. Two cardiothoracic anesthesiologists with extensive experience were directly involved in the perioperative management of each case and adhered to the institutional written guidelines [Figure 1].[15]

Study endpoints

In this STROBE compliant descriptive cohort study, we collected all data related to patient demographic and physical status, comorbidities, current medications, anesthetic and surgical management, as well as postoperative cardiac outcome during the primary hospitalization. These data were reported on a case report form and entered in an electronic database.

The diagnostic criteria of PCVD – the primary study endpoint – was the need for inotropic support for more than 120 min (dobutamine >5 mcg/kg/min, epinephrine >0.05 mcg/kg/min, milrinone >0.3 mcg/kg/min, and
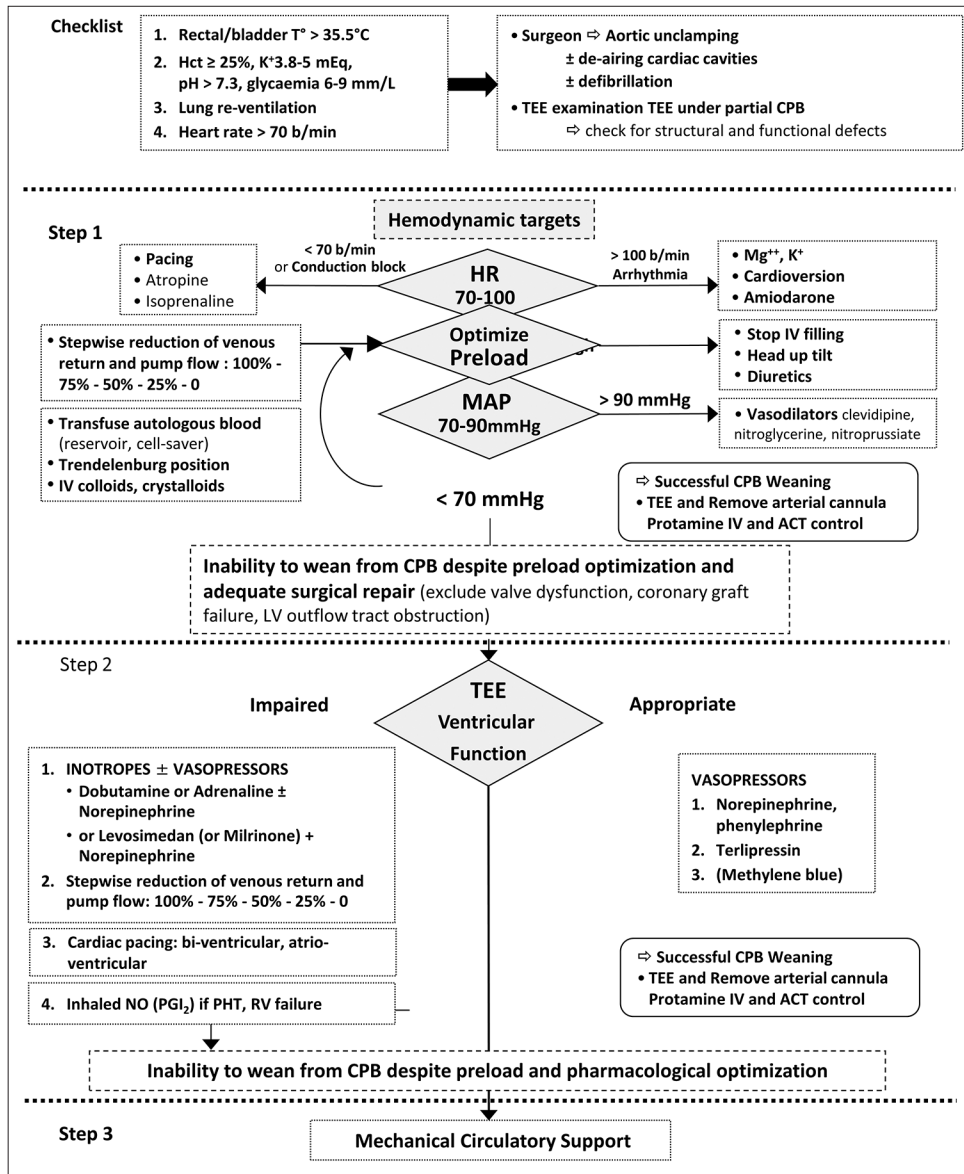
Figure 1: A standardized approach for weaning from bypass

norepinephrine >0.04 mcg/kg/min) in the presence of impaired ventricular function and a low MAP (<60 mmHg) despite adequate circulatory filling. Other causes of low arterial pressure such as hypovolemia and vasoplegic syndrome were excluded since these conditions could be corrected with fluid loading and vasopressor therapy, respectively.

As secondary clinical endpoints, we reported in-hospital mortality and the incidence of cardiovascular adverse events (myocardial infarct, atrial fibrillation, LCOS, and stroke), respiratory complications (atelectasis, pneumonia, and mechanical ventilation >24 h), renal dysfunction (reduction in estimated glomerular filtration >25%), re-operation, perioperative bleeding (requirement for >4 packed red blood cell transfusion), and the length of stay in the ICU and until hospital discharge. A modified version of the

Dindo-Clavien systemic classification was used to report major adverse events [Annex A].[16]

Statistical analysis

Perioperative clinical and surgical characteristics as well as postoperative outcome data of patients with and without PCVD were compared with the Chi-square test for categorical variables (expressed in percentage) and the Student's *t*-test (normal distribution) or Wilcoxon rank test (non-Gaussian distribution) for continuous variables (all expressed as mean ± standard deviation).

Variables that had a univariate $P < 0.15$ or those judged to be clinically important were selected for inclusion in a logistic regression model by stepwise forward selection. Only one variable in a set of variables with a correlation coefficient >0.5 was retained to avoid multicollinearity.

Independent predictors of PCVD and factor-adjusted odds ratios (ORs) with 95% confidence interval (CI) were calculated. All analyses were performed using STATA 14 software (Stata Corp., College Station, TX, USA) and statistical significance was specified as a two-tailed Type I error (*P* value) set below the 0.05 level.

Results

Over a 5-year period, 295 moderate-to-high risk patients were screened, 243 provided informed consent, 21 were excluded (study staff unavailable, *n* = 7; not meeting selection criteria, *n* = 14), and 222 with completed data were analyzed. In this cohort, 141 patients (64%) received intravenous inotropic drug support and 26 (12%) required assistance with an intra-aortic balloon pump counterpulsation. The criteria of PCVD were met in 63 patients (28.4%). Compared with the group without PCVD, patients with PCVD were significantly older, presented more often signs of heart failure and higher Parsonnet scores, had longer CPB and aortic clamping times, and received less frequently GIK before CPB [Table 1]. Other clinical and surgical data were similar in the two groups.

Of the 28 preoperative and intraoperative variables subjected to univariate analysis, nine demonstrated a significant association with the occurrence of PCVD: age older than 75 years, low body mass index, low LV ejection fraction (LVEF), elevated Parsonnet score, renal dysfunction, perioperative bleeding, a long bypass time or aortic clamping time, and the administration of GIK [Table 2]. A significant correlation was found between aortic clamping time and CPB time (R^2 = 0.731) and therefore only aortic clamping time was considered into the logistic regression model. Likewise, the Bernstein-Parsonnet score was not included in the model to avoid multicollinearity.

Logistic regression analysis identified five independent predictors of PCVD [Table 3]: prebypass GIK (OR = 0.14; 95% CI, 0.06–0.33), LVEF <40% (OR = 6.36; 95% CI, 2.59–15.60), age older than 75 years (OR = 3.35; 95% CI, 1.64–6.81), prolonged clamping time (OR = 3.72; 95% CI, 1.66–8.36), and perioperative bleeding (OR = 2.33; 95% CI, 1.01–5.41). This multivariate model for predicting LV dysfunction was accurate, with an area under the receiver operating characteristic curve of 0.81 and a Hosmer-Lemeshow goodness-of-fit value of 0.91 indicating good model calibration. There was no evidence that additional covariates would improve the model (*P* = 0.539 by the likelihood-ratio test).

Postoperative outcome data are shown in Table 4. Compared with patients without PCVD, those experiencing PCVD presented higher in-hospital mortality (12.7% vs. 0.6%, *P* < 0.001) with increased incidences of cardiovascular and respiratory complications as well as renal dysfunction. Noteworthy, among patients with PCVD,

myocardial infarct developed more frequently (19 [30.2%] vs. 12 [7.6%] in patients without PCVD) as well as a LCOS (24 [38.1%] vs. 11 [6.9%]). Furthermore, the need for prolonged mechanical ventilation and the ICU and hospital length of stay were significantly higher in patients with PCVD.

Discussion

In this cohort including moderate-to-high-risk patients scheduled for open heart surgery, 28% of them experienced PCVD and these patients had a prolonged stay in the ICU owing to more frequent cardiopulmonary complications and renal dysfunction compared with patients without PCVD. Advanced age, preoperative low LVEF, perioperative bleeding, and prolonged aortic clamping time were all identified as independent risk factors of PCVD whereas the administration of GIK before bypass was associated with myocardial protection.

The elevated risk profile of this cohort was mainly related to advanced age (63% ≥70 years) and a high prevalence of some comorbidities (hypertension in 93% of patients, LVEF <50% in 65%, diabetes mellitus in 28%, and chronic obstructive lung disease in 14%). According to a mean Parsonnet score of 21, the overall predicted mortality was 5.5%[17] and the lower observed mortality (4.0%) could partly be attributed to the perioperative protocol-driven approach where the anesthetic and surgical techniques were standardized and a goal-directed protocol based on TEE and hemodynamic monitoring was applied to separate patients from CPB.

In the current trial, the main study endpoint –PCVD – was clearly defined as the need for prolonged pharmacological inotropic support and was helpful to identify patients at risk for adverse postoperative clinical outcome. Weaning the patient from the CPB remains a critical phase where both the cardiac surgeon and the anesthesiologist share important information regarding the completeness of surgery and postischemic functional recovery of the heart. Within a short time, important decisions are taken regarding additional surgical interventions in case of ongoing myocardial ischemia, paravalvular regurgitation, or valve prosthesis mismatch.[18] Likewise, cardiovascular drugs are selectively prescribed and titrated to support the failing heart and to correct the vasoplegic syndrome that often occurs after myocardial ischemia-reperfusion.[10]

Although PCVD most often resolved within the first hours after surgery, in 30% of our surgical cases, PCVD forecasted the development of LCOS and it was associated with myocardial infarction and/or ischemia-reperfusion injuries as evidence by a larger release of cardiac troponin. The consequent mismatch between oxygen supply and metabolic requirements was also manifested by decreased glomerular filtration rate and impaired respiratory muscle function along with a

Table 1: Baseline preoperative and intraoperative characteristics of patients undergoing open cardiac surgery and presenting or not postcardiotomy ventricular dysfunction

Preoperative	All (*n*=222)	PCVD (*n*=63)	No PCVD (*n*=159)	*P*
Demographic and clinical data				
Age (years)*	71.3 (10.7)	74.3 (10.1)	70.1 (10.7)	<0.001†
Weight (kg)*	79.9 (14.7)	78.8 (15.4)	80.4 (14.4)	0.472†
Height (cm)*	169.4 (8.6)	170.1 (8.8)	169.1 (8.5)	0.446†
Body mass index*	27.9 (5.0)	27.3 (5.5)	28.1 (4.7)	0.281†
Sex (male)	153 (68.9)	43 (68.3)	110 (69.0)	0.893
Hypertension	206 (92.8)	59 (93.7)	147 (92.5)	0.756
Pulmonary hypertension	22 (9.9)	10 (15.9)	12 (7.6)	0.061
Diabetes mellitus	84 (37.8)	25 (39.7)	59 (37.1)	0.721
Vascular disease	93 (41.9)	25 (39.7)	68 (42.8)	0.674
Chronic obstructive lung disease	31 (14.0)	7 (11.1)	24 (15.1)	0.440
Karnofsky performance status <50	25 (11.3)	9 (14.3)	16 (10.1)	0.370
Previous cardiac surgery	15 (6.8)	1 (1.6)	14 (8.8)	0.053
NYHA class‡	2 (2-3)	2 (2-4)	2 (2-3)	0.041§
LVEF (%)*	45.0 (9.6)	41.9 (11.2)	46.3 (6.9)	0.003†
Parsonnet score*	21.2 (8.3)	24.0 (7.6)	20.0 (8.4)	0.001†
Chronic preoperative medications				
Beta-blockers	114 (51.4)	34 (54.0)	80 (80.3)	0.623
Calcium antagonists	28 (12.6)	6 (9.5)	22 (13.8)	0.383
ACEI or angiotensin-II blocker	102 (46.0)	23 (36.5)	79 (49.7)	0.076
Diuretics	76 (34.2)	26 (41.3)	50 (31.5)	0.164
Anti-platelets	148 (66.7)	38 (60.3)	110 (69.2)	0.207
Blood parameters				
Hemoglobin (g/dL)*	12.2 (2.1)	11.9 (2.2)	12.3 (2.0)	0.211†
Creatinine clearance (mL/min)*	92.8 (39.9)	84.9 (40.2)	95.9 (39.5)	0.067†
Intraoperative	**All (*n*=222)**	**PCVD (*n*=63)**	**No PCVD (*n*=159)**	**P**
Type of surgery				
Aortic valve replacement	107 (48.2)	30 (47.6)	77 (48.4)	0.913
Coronary artery bypass graft	81 (36.5)	33 (33.3)	60 (37.7)	0.539
Combined	34 (15.3)	12 (19.1)	22 (13.8)	0.331
Surgical time				
CPB time (min)*	108.5 (46.5)	128.2 (55.6)	100.7 (40.1)	<0.001†
Aortic clamping time (min)*	77.1 (34.4)	89.1 (38.6)	72.4 (31.6)	0.001†
Fluids				
Crystalloids (mL)*	2808 (1090)	3017 (1106)	2725 (1075)	0.072
Crystalloids (mL/min)*	12.5 (5.1)	12.2 (5.5)	12.6 (4.9)	0.628
Colloids (ml)*	280 (452)	298 (477)	273 (442)	0.702
Colloids (mL/min)*	1.1 (1.8)	1.1 (2.1)	1.1 (1.8)	0.905
Blood transfusion	148 (66.7)	41 (65.1)	107 (67.3)	0.752
Fresh frozen plasma	65 (29.3)	22 (34.9)	43 (27.0)	0.245
Platelets	36 (16.2)	13 (20.6)	23 (14.5)	0.261
GIK before CPB	110 (50.0)	18 (28.6)	92 (57.9)	<0.001

Data given as *n* (%) unless otherwise indicated. Chi-squared tests were used for statistical tests unless otherwise indicated. *Data given as mean (SD), †Student's *t*-test, ‡Data given as median (range), §Wilcoxon rank-sum test. ACEI: Angiotensin converting enzyme inhibitor, CPB: Cardiopulmonary bypass, PCVD: Postcardiotomy ventricular dysfunction, NYHA: New York Heart Association, GIK: Glucose-insulin-potassium, LVEF: Left ventricular ejection fraction, SD: Standard deviation

prolonged need for mechanical ventilation and a higher propensity for pulmonary complications. Moreover, the perioperative use of inotropes could further contribute to worsen postoperative clinical outcome as reported in several large cohort studies where inotrope therapy has been identified as a risk factor of postoperative mortality and cardiovascular complications.[19-21] Indeed, catecholamines may transiently enhance postischemic functional recovery and accelerate weaning from bypass; however, by promoting insulin resistance and fatty acid oxidation (instead of glucose utilization), the administration of catecholamines increases myocardial

Table 2: Effect of patient characteristics and perioperative management on the occurrence of postcardiotomy ventricular dysfunction

Preoperative patient characteristics	PCVD		OR	95% CI	*P*
	Yes, *n* (%)	No, *n* (%)			
Age >75 (years)					
Yes	38 (40.4)	56 (59.6)	2.80	1.51-5.19	<0.001
No	25 (19.5)	103 (80.5)	1.00	Reference	-
Body mass index					
>21-30	40 (28.2)	102 (71.8)	1.00	Reference	-
>30	18 (25.0)	54 (75.0)	0.85	0.44-1.93	0.623
≤21	5 (62.5)	3 (37.5)	4.22	0.94-19.12	0.040
Sex					
Male	43 (28.1)	110 (71.9)	1.00	Reference	-
Female	20 (29.0)	49 (71.0)	1.04	0.56-1.96	0.893
High blood pressure					
Yes	59 (28.6)	147 (71.4)	1.20	0.37-3.90	0.756
No	4 (25.0)	12 (75.0)	1.00	Reference	-
Pulmonary hypertension					
Yes	10 (45.5)	12 (54.6)	2.31	0.93-5.71	0.062
No	53 (26.5)	147 (73.5)	1.00	Reference	-
Diabetes					
Yes	25 (29.8)	59 (70.2)	1.12	0.61-2.03	0.722
No	38 (27.5)	100 (72.5)	1.00	Reference	-
Vascular disease					
Yes	25 (26.9)	68 (73.1)	0.88	0.49-1.60	0.675
No	38 (29.5)	91 (70.5)	1.00	Reference	-
Chronic obstructive lung disease					
Yes	7 (22.6)	24 (77.4)	0.70	0.29-1.73	0.441
No	56 (29.3)	135 (70.7)	1.00	Reference	-
Karnofsky performance status <50					
yes	9 (36.0)	16 (64.0)	1.49	1.69-3.58	0.371
No	54 (27.4)	143 (72.6)	1.00	Reference	-
Parsonnet score >22					
Yes	40 (40.8)	58 (59.2)	3.03	1.62-5.67	<0.001
No	23 (18.6)	101 (81.5)	1.00	Reference	-
LVEF <40%					
Yes	25 (51.0)	23 (49.0)	3.70	1.85-7.40	<0.001
No	38 (22.0)	135 (78.0)	1.00	Reference	-
NYHA class ≥3[#]					
Yes	22 (36.7)	38 (63.3)	1.71	0.90-3.24	0.096
No	41 (25.3)	121 (74.7)	1.00	Reference	-
Anemia (Hb <100g/l)					
Yes	12 (42.9)	16 (57.1)	2.10	0.92-4.78	0.070
No	51 (26.3)	143 (73.7)	1.00	Reference	-
Renal insufficiency (eGFR <60)					
Yes	18 (41.9)	25 (58.1)	2.14	1.06-4.33	0.029
No	45 (25.1)	134 (74.9)	1.00	Reference	-
Chronic preoperative medications					
Beta-blockers					
Yes	34 (29.8)	80 (70.2)	1.16	0.64-2.08	0.624
No	29 (26.9)	79 (73.2)	1.00	Reference	-
Calcium antagonists					
Yes	6 (21.4)	22 (78.6)	0.66	0.25-1.71	0.384
No	57 (29.4)	137 (70.6)	1.00	Reference	-

Contd...

Preoperative patient characteristics	PCVD		OR	95% CI	*P*
	Yes, *n* (%)	No, *n* (%)			
ACEI or angiotensin-II blocker					
Yes	23 (22.6)	79 (77.5)	0.58	0.32-1.07	0.076
No	40 (33.3)	80 (66.7)	1.00	Reference	-
Diuretics					
Yes	26 (34.2)	50 (65.8)	1.53	0.83-2.81	0.165
No	37 (25.3)	109 (74.7)	1.00	Reference	-
Anti-platelets					
Yes	38 (25.7)	110 (74.3)	0.68	0.37-1.25	0.201
No	25 (33.8)	49 (66.2)	1.00	Reference	-
Surgical and intraoperative characteristics	**PCVD**		**OR**	**95% CI**	***P***
	Yes, *n* (%)	No, *n* (%)			
Type of surgery					
CABG	21 (25.9)	60 (74.1)	1.00	Reference	-
AVR	30 (28.0)	77 (72.0)	1.11	0.58-3.13	0.747
Combined	12 (35.3)	22 (64.7)	1.56	0.66-3.69	0.313
Previous cardiac surgery					
Yes	1 (36.0)	14 (64.0)	0.17	0.02-1.33	0.054
No	62 (27.4)	145 (72.6)	1.00	Reference	-
Bleeding					
Yes	16 (42.1)	22 (57.9)	2.12	1.02-4.41	0.040
No	47 (25.5)	137 (74.5)	1.00	Reference	-
Long aortic clamping time*					
Yes	24 (45.3)	29 (54.7)	2.76	1.42-5.36	<0.001
No	39 (23.1)	130 (76.9)	1.00	Reference	-
Long CBP time**					
Yes	23 (43.4)	30 (56.6)	2.42	1.26-4.79	0.006
No	40 (23.7)	129 (76.3)	1.00	Reference	-
Prebypass GIK					
Yes	18 (16.4)	92 (83.6)	0.29	0.15-0.56	<0.001
No	45 (40.2)	67 (59.8)	1.00	Reference	-
Blood transfusion					
Yes	41 (27.7)	107 (72.3)	0.91	0.49-1.68	0.753
No	22 (29.7)	52 (70.3)	1.00	Reference	-
Fresh frozen plasma					
Yes	22 (33.9)	43 (66.2)	1.45	0.77-2.71	0.246
No	41 (26.1)	116 (73.9)	1.00	Reference	-
Platelets					
Yes	13 (36.1)	23 (63.9)	1.54	0.72-3.28	0.262
No	50 (26.9)	136 (73.1)	1.00	Reference	-
Fluids (>12.5 mL/min)					
Yes	26 (23.4)	85 (76.6)	0.61	0.34-1.11	0.102
No	37 (33.3)	74 (66.7)	1.00	Reference	-

*>75 percentile stratified for surgery: CABG >80 min, AVR >96 min; combined >120 min, **>75 percentile stratified for surgery: CABG >120 min, AVR >127 min; combined >160 min. ACEI: Angiotensin-converting enzyme inhibitors, eGFR: Estimated glomerular filtration rate, Hb: Hemoglobin, NYHA: New York Heart Association functional classification of heart failure, CABG: Coronary artery bypass graft, AVR: Aortic valve replacement, CPB: Cardiopulmonary bypass, PCVD: Postcardiotomy ventricular dysfunction, OR: Odds ratio, CI: Confidence interval, GIK: Glucose-insulin-potassium, LVEF: Left ventricular ejection fraction

oxygen consumption and deplete energetic substrates within the cardiomyocytes.[22] Consequently, short-term hemodynamic improvement can be outweighed by adverse events related to arrhythmias, hyperglycemia, lactic acidosis, and beta-adrenergic receptor desensitization.

The risk factors for PCVD in the current study were similar to those reported for LCOS in previous studies,[3,6,23] and this emphasizes the clinical and pathophysiological continuum between these two entities. Preoperative risks factors such as advanced age and low LVEF are not

amenable to optimization therapies. Experimental evidence supports that the senescent hearts are more vulnerable to ischemic insults while being also more refractory to protective interventions.[24] Likewise, in patients with low LVEF, the wide range in myocardial viability due to remodeling and fibrotic changes results in a greater propensity to ischemia-reperfusion injuries.[25] Importantly, these "non-modifiable" factors are also included in the popular risk scoring systems (e.g., EuroScore, Parsonnet, Society of Thoracic Surgery) as risk factors to predict mortality after cardiac surgery and therefore might be

useful to select the surgical candidates and to rationalize resources utilization in the hospital.[17,26]

It is worth mentioning that these current risk classification systems do not consider the intraoperative time course which can be a decisive factor for the postoperative patient's clinical outcome.[27] In the present trial, we found that the duration of aortic cross-clamping and perioperative bleeding were predictors of PCVD. Interestingly, these intraoperative factors can be modified by implementing dedicated protocols and by improving the expertise, the skills and experience of the heart team. Aortic cross-clamping time reflects ischemic injury and despite modern myocardial protection techniques, it remains a prominent mechanism leading to LCOS regardless of the preoperative LVEF.[28-30] Noteworthy, prolonged aortic clamping times and perioperative bleeding may also denote technical difficulties in executing the planned operation because of unfavorable anatomy or intraoperative complications. Besides perioperative bleeding, preoperative anemia and low hematocrit during CPB have also been identified as modifiable risk factors of postoperative mortality, renal failure and cardiovascular morbidity.[31]

These intraoperative factors are closely related since both CPB and myocardial ischemia-reperfusion trigger a systemic inflammatory response manifested by a hyperdynamic circulatory state, alteration in platelet

Table 3: Logistic regression analysis showing the adjusted odds ratios for variables independently associated with the occurrence of postcardiotomy ventricular dysfunction

	Adjusted OR	95% CI	$P^{\#}$
GIK	0.14	0.06-0.33	<0.001
LVEF <40%	6.36	2.59-15.60	<0.001
Age >75 (years)	3.35	1.64-6.81	<0.001
Prolonged aortic cross-clamping*	3.72	1.66-8.36	<0.001
Perioperative bleeding	2.33	1.01-5.41	0.048

*>75 percentile stratified for surgery: CABG >80 min, AVR >96 min; combined >120 min, #Wald test. CI: Confidence interval, OR: Odds ratio, CABG: Coronary artery bypass surgery, AVR: Aortic valve replacement, GIK: Glucose-insulin-potassium, LVEF: Left ventricular ejection fraction

Table 4: Outcome of patients with and without postcardiotomy ventricular dysfunction

Outcome	All (*n*=222)	PCVD (*n*=63)	No PCVD (*n*=159)	*P*
Mortality	9 (4.5)	8 (12.7)	1 (0.6)	<0.001°
AVR	2 (1.9)	2 (6.7)	0	0.077°
CABG	3 (3.7)	3 (14.3)	0	0.016°
Combined surgery	4 (11.8)	3 (25.0)	1 (4.6)	0.115°
Cardiovascular complications				
Atrial fibrillation	98 (44.1)	34 (54.0)	64 (40.3)	0.064
Low cardiac output syndrome	35 (15.8)	24 (38.1)	11 (6.9)	<0.001
Myocardial infarct	31 (14.0)	19 (30.2)	12 (7.6)	<0.001
Stroke	10 (4.5)	2 (3.2)	8 (5.0)	0.729
Troponin I (day 1) (µg/L)‡	3.4 (1.8-6.4)	5.3 (3.0-14.3)	3.1 (1.6-5.8)	<0.001§
Respiratory complications				
Atelectasis	76 (34.2)	31 (49.2)	45 (28.3)	<0.001
Pneumonia	20 (9.0)	13 (20.6)	7 (4.4)	<0.001
Ventilation >24 h	95 (42.8)	44 (69.8)	51 (32.1)	<0.001
Renal dysfunction				
Reduction in GFR >25%	44 (19.8)	20 (31.8)	24 (15.1)	0.005
Surgical complications				
Bleeding	38 (17.1)	16 (25.4)	22 (13.8)	0.039
Need for redo surgery	17 (7.7)	7 (6.3)	10 (11.1)	0.771
Length of stay (days)				
ICU‡	3 (2-5)	5 (3-11)	3 (2-4)	<0.001§
Hospital‡	15 (12-21)	20 (15-27)	14 (11-17)	<0.001§

Data given as *n* (%) unless otherwise indicated. Chi-squared tests were used for statistical tests unless otherwise indicated. ‡Data given as median (range), §Wilcoxon rank sum test, °Fisher's exact test. PCVD: Postcardiotomy ventricular dysfunction, CABG: Coronary artery bypass surgery, AVR: Aortic valve replacement, GFR: Glomerular filtration rate, ICU: Intensive Care Unit

function and coagulation factors, activation of leucocytes and endothelial cells, as well as the release of cytokines and oxygen free radicals.[11] Therefore, prolonged duration of CPB and aortic cross-clamping has been associated not only with PCVD but also with more frequent pulmonary complications, larger requirement for transfusion, and renal impairment.[28] Besides standard anterograde blood cardioplegia, the implementation of GIK before CPB was associated with a marked attenuation of the PCVD, supporting the growing body of scientific knowledge on GIK-induced myocardial protection.[32,33] The enhanced postischemic ventricular function could be attributed to the higher glycogen stores as the energetic pathway can be switched from fatty acids to glucose oxidation when the GIK metabolic cocktail is given before ischemia.[34,35]

There are some limitations in our study. First, our study remains retrospective despite the fact that all data were prospectively collected, and as such, we can only report on associations rather than causality between the PCVD and the reported risk factors. Second, potential risk factors such as preoperative renal dysfunction, frailty or functional dependency, diabetes, vascular disease, or prior cardiac surgery could not be analyzed given the relatively small sample size of the study population and the low prevalence of some comorbidities. Likewise, patients with severe organ failure were excluded and exploring the impact of critical concomitant illnesses would deserve larger cohorts with a wider range of pathologies. Finally, the limitations related to this single-center study, its retrospective design, and the small sample preclude generalizability of our results.

Conclusions

Our data indicate that age, duration of aortic cross-clamping, and preexisting LV systolic dysfunction are independent risk factors for early PCVD whereas the administration of GIK is association with a lower incidence of PCVD in moderate-to-high risk patients undergoing AVR or coronary artery bypass graft surgery. These data strengthen the need for randomized controlled trials testing perioperative management strategies aimed to target modifiable risk factors in patients undergoing cardiac surgery.

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Conflicts of interest

There are no conflicts of interest.

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Annex A: Modified classification system of postoperative complications*

	Cardiovascular	Pulmonary	Renal	Others
Grade I: Transient, self-limiting AE	Nonsustained arrhythmias Hypotension associated with anesthesia induction or mild hypovolemia	Mild hypoxemia responsive to O_2 therapy (<0.3 FiO_2)	<25% decrease in eGFR	
Grade II: AE requiring pharmacologic treatment or minor intervention	Arrhythmias requiring pharmacologic treatment Hypotension associated with mild hypovolemia	Moderate hypoxemia, atelectasis requiring CPAP support		Superficial SSI
Grade IIIa: AE event requiring intervention without sedation/general anesthesia or potentially causing disability	Arrhythmias requiring electrical cardioversion Hypovolemia requiring aggressive fluid management Myocardial ischemia Transient cerebral ischemia	Atelectasis requiring bronchoscopy or intense chest therapy Moderate-severe Hypoxemia requiring NIV support Pneumonia	25%-50% decrease in eGFR	Deep SSI
Grade IIIb: AE requiring intervention under sedation/general anesthesia or causing disability	Myocardial infarct (mild) Stroke New or worsening heart failure, LCOS requiring pharmacological support (1 drug)	Severe hypoxemia requiring NIV support (ALI/ARDS, pneumonia, heart failure, muscle failure)	>50% decrease in eGFR	Mediastinitis
Grade IVa: Admission in ICU for single organ dysfunction	New or worsening heart failure, LCOS requiring intense pharmacological support (>2 drugs) and/or mechanical assistance Recurrent or sustained arrhythmias Myocardial ischemia/infarct (extensive)	Severe hypoxemia requiring intubation and mechanical ventilator support (ALI/ARDS, pneumonia, heart failure, muscle failure)	Renal failure requiring hemodialysis or hemofiltration	
Grade IVb	Cardiac arrest with resuscitation			Combined organ dysfunction

SSI: Surgical site infection, AE: Adverse event, eGFR: Estimated glomerular filtration rate, CPAP: Continuous positive airway pressure, NIV: Noninvasive ventilation, ALI: Acute lung injury, ARDS: Acute respiratory distress syndrome, LCOS: Low cardiac output syndrome