The Heart Surgery Forum 2022-4449
25 (6), 2022 [Epub November 2022]
doi: 10.1532/hsf.4449
Online address: http://journal.hsforum.com

Incomplete Pericardial Dissection, Fluid Overload, Delayed Diagnosis And Treatment, And Tuberculosis Pericarditis Are Associated With Low Cardiac Output Syndrome Following Pericardiectomy

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ABSTRACT

Background: We aimed to investigate risk factors of LCOS following pericardiectomy.

Methods: This was a retrospective study of patients undergoing pericardiectomy at three hospitals between January 1994 and May 2021.

Results: A total of 826 patients were divided into two groups: group with LCOS (N = 126) and group without LCOS (N = 700). The incidence of postoperative LCOS was 15.3%. There were 66 operative deaths (8.0%). Univariable and multivariable analyses showed that factors are associated with LCOS, including postoperative LVEDD (P < 0.001), preoperative LVEDD (P < 0.001), time between symptoms and surgery (P < 0.001), thickness of pericardium (P < 0.001), intubation time (P = 0.002), hospitalized time postoperative (P < 0.001), preoperative central venous pressure (P = 0.016), postoperative central venous pressure (P = 0.034), D0 fluid balance (P = 0.019), D2 fluid balance (P = 0.017), postoperative chest drainage (P < 0.001), surgical duration (P < 0.001), bleeding during operation (P = 0.001), serum creatinine 24h after surgery (P < 0.001), serum creatinine 48h after surgery (P = 0.017), fresh-frozen plasma (P = 0.005), packed red cells (P = 0.006), and tuberculosis pericarditis (P = 0.026).

Conclusion: In our study, incomplete pericardial dissection, fluid overload, delayed diagnosis and treatment, and tuberculosis pericarditis are associated with LCOS following pericardiectomy.

Received November 28, 2021; received in revised form February 15, 2022; accepted September 29, 2022.

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INTRODUCTION

Constrictive pericarditis is the result of chronic inflammation characterized by fibrous thickening and calcification of the pericardium that injures diastolic filling, decreases cardiac output, and ultimately results in heart failure [Melo 2019].

Low cardiac output syndrome (LCOS) is associated with increased risk of mortality and morbidity. Determining the risk factors of LCOS has clinical significance for the management of LCOS. The important roles of pericardiectomy include removal of the fibrous thickened pericardium, recovering cardiac diastolic filling and increasing cardiac output. Identifying the risk factors would allow to develop strategies aiming to reduce morbidity and mortality. Some clinical predictors of LCOS have been reported, including left ventricular ejection fraction <30%, female gender, surgical history, and increasing age [Bautista-Hernandez 2016]. The objective of this study was to determine the risk factors of low cardiac output syndrome following pericardiectomy. We hypothesize that the incomplete pericardial dissection, fluid overload, delayed diagnosis and treatment, and tuberculosis pericarditis are associated with LCOS following pericardiectomy.

PATIENTS AND METHODS

Design: This was a retrospective, observational cohort study of patients undergoing pericardiectomy between January 1994 and May 2021 at The People's Hospital of Guangxi Zhuang Autonomous Region, Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, and The People's Hospital of Liuzhou City. Medical records were reviewed.

Inclusion criteria: Patients undergoing pericardiectomy between January 1994 and May 2021 at The People's Hospital of Guangxi Zhuang Autonomous Region, Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, and The People's Hospital of Liuzhou City.

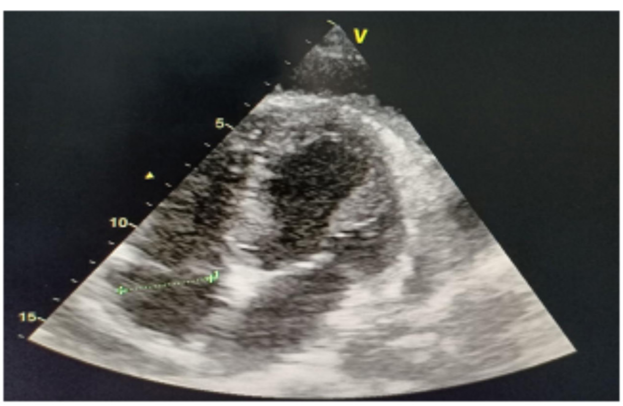
Exclusion criteria: Patients with missing medical records. Variables were evaluated. (A supplemental)

Variables to be analyzed – low cardiac output syndrome: All patients were monitored with a pulmonary artery catheter in the operation room and intensive care unit, and cardiac output (CO) and venous oxygen saturation of hemoglobin continuously were measured. Low cardiac output syndrome is defined by a cardiac index (CI) of less than 2.0 L/min/m2 in the operation room and intensive care unit. LCOS is characterized by clinical signs or symptoms, including elevated blood lactate or rapid increase in blood lactate, decreased central venous oxygen saturation, increased arterial to central venous oxygen saturation difference, decreased urine output, increased peripheral skin temperature to core body temperature difference, and low echocardiographic Doppler-derived cardiac index, high inotrope requirement [Du 2020; Chandler 2016].

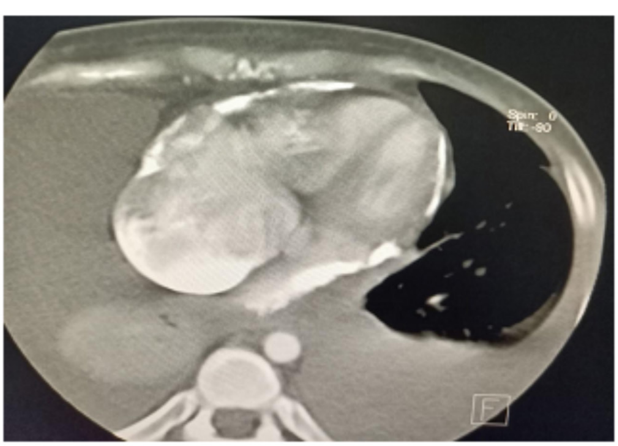
Preoperative diuresis protocol: Hydrochlorothiazide tablet 25mg bid, furosemide tablet 20mg bid. Diuresis treatment lasted 7 to 30 days.

Postoperative LVEDD was measured by transthoracic echocardiography postoperatively 1 to 7 days in the intensive care unit.

Perioperative death was defined as death within 30 days of the operation or during the same hospital admission.



a. Transthoracic echocardiography shows the thickened pericardium.



b. Chest computed tomographic scan shows the significantly thickened and calcified ring of pericardium.

Figure 1. The thickened pericardium

In our study, serum creatinine was used as the diagnostic standard of acute renal injury. According to Kidney Disease Improving Global Outcomes (KDIGO) classification, if serum creatinine increases by ≥ 0.3 mg/dl (26.5 μmol/l) within 48 hours, serum creatinine is 50% higher than the baseline within first seven days, or urine output is below 0.5 ml/kg/hour for six hours, the patient is considered to have acute renal injury [Howitt 2018].

Multiorgan failure (MOF) is regarded as a continuous process of varying levels of organ failure rather than an all-or-none event. To characterize MOF, six different organ systems are regarded as key organs: lungs, cardiovascular system,

Table 1. Preoperative characteristics of the patients (N = 826)

Variable	Value
Female/male, n	280/546
Age, years	53.9±0.6 (range, 17.0 to 73.0)
Weight before diuresis, kg	56.1±0.4 (range, 36.0 to 80.0)
Weight after diuresis, kg	53.8±0.4 (range, 34.0 to 75.0)
Time between symptoms and surgery, months	9.3±0.9 (range, 0.3 to 120.3)
BMI before diuresis, kg/m^2	21.9±0.1 (range, 15.4 to 31.3)
BMI after diuresis, kg/m^2	21.0±0.1 (range, 14.5 to 28.2)
NYHA class	
II, n (%)	462 (55.9%)
III, n (%)	347 (42.0%)
IV, n (%)	17 (2.1%)
Cachexia, n (%)	33 (4.0%)
Pulmonary tuberculosis, n (%)	17 (2.1%)
Rheumatic heart disease, n (%)	33 (4.0%)
Infective endocarditis, n (%)	9 (1.1%)
Valvular heart disease, n (%)	34 (4.1%)
Coronary heart disease, n (%)	28 (3.4%)
Pleural effusion, n (%)	74 (9.0%)
Preoperative LVEDD, mm	41.7±0.2 (range, 29.0 to 60.0)
Preoperative LVEF, %	62.5±0.3 (range, 51.0 to 77.0)
Aortic insufficiency, n (%)	58 (7.0%)
Mitral regurgitation, n (%)	70 (8.5%)
Preoperative tricuspid insufficiency, cm^2	1.8±0.1 (range, 0.0 to 13.5)
Thickened pericardium, n (%)	825 (99.9%)
Thickness of pericardium, mm	20.2±0.3 (range, 3.0 to 30.0)
Tuberculosis pericarditis, n (%)	434 (52.5%)
Pericardial effusion, n (%)	406 (49.2%)
Pericardial calcification, n (%)	196 (23.7%)
Patients with CPB, n (%)	76 (9.2%)

BMI, weight/($height^2$), (kg/m^2)

kidneys, liver, coagulation system, and the central nervous system [Durham 2003].

Hepatic failure is defined as "a severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy within 8 weeks of the first symptoms in the absence of pre-existing liver disease [Bernal 2013].

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchange functions, i.e. oxygenation of and/or elimination of carbon dioxide from mixed venous blood. It is defined by an arterial oxygen tension (Pa,O2) of ≤ 8.0 kPa (60 mmHg), an arterial carbon dioxide tension (Pa,CO2) of ≥6.0 kPa (45 mmHg) or both [Roussos 2003].

Table 2. Preoperative data

Variable	Group with LCOS (*N* = 126)	Group without LCOS (*N* = 700)	*P*-value
Male, n (%)	56 (44.4%)	490 (70.0%)	<0.001
Age, years	52.5±2.1	54.1±0.7	0.412
Time between symptoms and surgery, months	23.3±4.3	6.7±0.7	<0.001
Weight before diuresis, kg	53.3±1.2	56.4±0.6	0.018
Weight after diuresis, kg	51.2±0.8	54.1±0.4	0.011
Height, cm	154.5±1.4	160.7±0.4	<0.001
BMI before diuresis, kg/m^2	22.4±0.4	21.8±0.1	0.095
BMI after diuresis, kg/m^2	21.6±0.3	20.9±0.1	0.058
Thickness of pericardium, mm	22.7±0.6	19.7±0.3	<0.001
Preoperative CVP, mmHg	25.1±0.0	19.2±0.2	<0.001
Preoperative LVEDD, mm	39.5±0.6	42.0±0.2	<0.001
Preoperative LVEF, %	63.3±1.0	62.4±0.3	<0.001
Tuberculosis pericarditis, n	84 (19.4%)	42 (10.7%)	<0.001

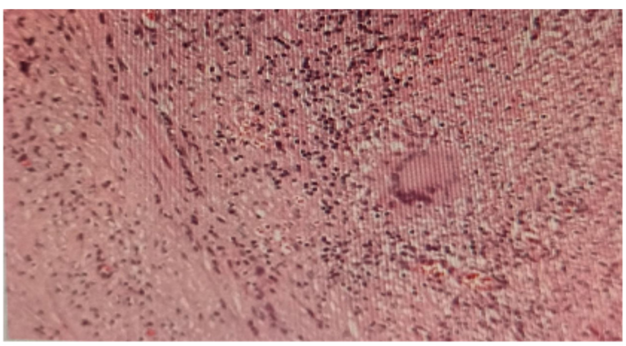
Table 3. Operative data

Variable	Group with LCOS (*N* = 126)	Group without LCOS (*N* = 700)	*P*-value
Operative death, n	66	0	<0.001
Bleeding during operation, ml	516.7±29.1	388.0±15.4	0.001
Surgical duration, mins	230.4±6.6	174.4±2.7	<0.001
Intubation time, hours	149.2±12.3	56.4±2.7	<0.001
ICU retention time, days	12.7±1.3	4.5±0.1	<0.001
Hospitalized time postoperative, days	24.5±3.7	14.8±0.3	<0.001
Postoperative CVP, mmHg	13.3±0.2	11.5±0.2	<0.001
D0 fluid balance, ml	-647.6±61.0	-1214.2±40.5	<0.001
D1 fluid balance, ml	-511.0±239.4	-534.6±39.8	0.856
D2 fluid balance, ml	-1140.0±153.3	-468.4±26.0	<0.001
Chest drainage, ml	1331.0±88.5	766.7±21.7	<0.001
Postoperative LVEDD, mm	40.2±0.4	43.9±0.2	<0.001
Postoperative LVEF, %	64.2±1.6	64.4±0.3	0.863
Adrenaline, %	100% (63/63)	19.9% (93/468)	<0.001
Dose of adrenaline, µg/kg/min	1.8±0.03	0.02±0.00	<0.001
Blood lactate, mmol/L	12.4±0.5	2.1±0.1	<0.001

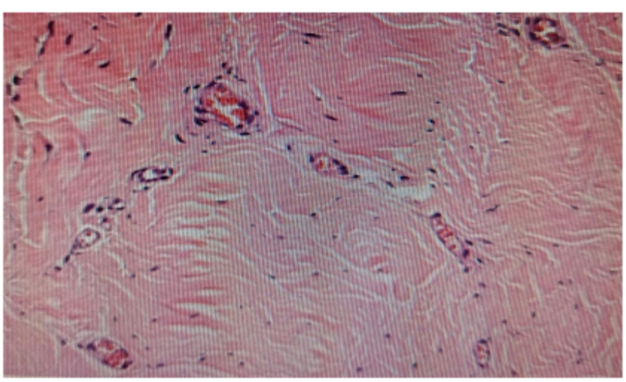
D0, fluid balance on operation day; D1, fluid balance postoperative day 1; D2, fluid balance postoperative day 2

Table 4. Use of inotropic medication (n=826)

Inotropic medication	Group with LCOS (*N* =126)	Group without LCOS (*N* = 700)
Dopamine	421	56
Milrinone	10	7
Dopamine+milrinone	55	0
Dopamine+adrenaline	131	0
Dopamine+adrenaline+milrinone	112	0
Dopamine+adrenaline+milrinone+norepinephrine	14	0
Dopamine+norepinephrine+milrinone+levosimendan	12	0
Dopamine+adrenaline+norepinephrine	8	0



a. Histopathologic studies of pericardium tissue show the characteristic histopathologic features of tuberculosis including typical granuloma and caseous necrosis.



b. Histopathologic studies of pericardium tissue show the histopathologic findings of chronic nonspecific inflammatory changes.

Figure 2. Histopathologic studies of pericardium tissue

Table 5. Operative results (*N* = 826)

Variable	Preoperative	Postoperative	*P*-value
CVP, mmHg	19.9±0.2	11.7±0.1	<0.001
LVEDD, mm	41.8±0.2	43.7±0.2	<0.001
LVEF, %	62.4±0.3	64.4±0.3	<0.001
TI,cm^2	1.8±0.1	1.7±0.1	0.210

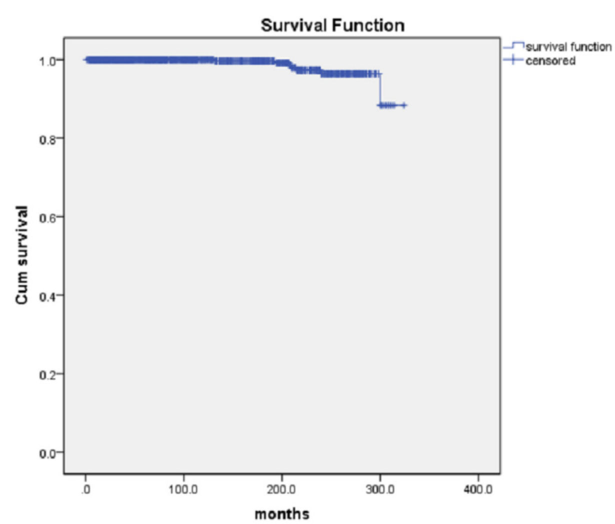


Figure 3. Kaplan-Meier curve for survival

Surgical technique: Pericardiectomy was performed via sternotomy, the pericardium was removed between the two phrenic nerves and from the great vessels to the basal aspect of the heart. Constricting layers of the epicardium were removed, when possible. The pericardium was palpated to identify a relatively soft and uncalcified area after median sternotomy, and the thymus removed laterally. An #-shaped incision was made over the pericardium. Dissection was started at the base of the aorta, extended downward to the lateral and posterior walls of the left ventricle, followed by the diaphragmatic pericardium. The pericardium over the right atrium and venae cavae was resected last. The myocardium was then exposed, to achieve mobilization of the heart down to the phrenic nerves. If calcified plaques penetrating the epicardium were present, we left small "islands" of calcified pericardial tissue. Cardiopulmonary bypass (CPB) was avoided during surgery except for concomitant valve replacement. (Table 2)

Table 6. Postoperative mortality and complications (*N* = 826)

Causes of postoperative mortality	Group with LCOS (*N* = 126)	Group without LCOS (*N* = 700)
Cardiogenic shock+AKI+ventricular fibrillation	12	0
Cardiogenic shock+AKI	36	0
Cardiogenic shock+AKI+hepatic failure+septicemia	8	0
Cardiogenic shock +AKI+respiratory failure	10	0
Complication		
Acute renal injury, n	186	36
Multiorgan failure, n	86	0
Long-term intubation >48h, n	321	72
Empyema, n	8	1
Hepatic failure, n	9	0
Respiratory failure	14	0
Ventricular fibrillation, n	16	0
Reoperation, n	5	0
Concomitant cardiac procedures undergoing CPB		
Constrictive pericarditis+rheumatic heart disease	16	17
Constrictive pericarditis+valvular heart disease	15	19
Constrictive pericarditis+infective endocarditis	5	4

Statistical analyses: Continuous variables are reported as means±SE. Survival rates were estimated using the Kaplan-Meier method. The chi-square test, Kruskal-Walls test or Wilcoxon rank-sum test, as appropriate, were used to evaluate relationships between the preoperative variables and select intraoperative and postoperative variables. The relationships with perioperative risk factors were assessed by means of contingency table methods and logistic regression analysis. P-values less than 0.05 were considered statistically significant. All analyses were performed using IBM SPSS version 24.0 software (IBM SPSS Inc., USA).

Univariable logistic regressions with LCOS as an outcome were analyzed first. Then, the Variance Inflation Factor was calculated to explore the independence of the selected variables. The results are listed in Table 7, and there is no evidence to show dependence among the selected factors. (Table 7) Therefore, the significant variables were entered into multiple logistic regressions without an interaction term, and the stepwise variable selection method was used to identify the potential risk factors of LCOS.

Ethics approval: The experiment protocol for involving humans was in accordance with the Helsinki Statement and national guidelines and was approved by the Medical Ethics Committee of The People's Hospital of Guangxi Zhuang Autonomous Region, Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, and The People's Hospital of Liuzhou City. They gave the authors approval to waive the need for patient consent for publishing data in the study about the patients.

RESULTS

Characteristics of the population under study: During the study period, 829 patients underwent pericardiectomy. Of this total, three met the exclusion criteria, so a total of 826 patients were eligible and included in the study group.

Diagnosis of constrictive pericarditis: The diagnosis of constrictive pericarditis was made on the basis of clinical manifestation, echocardiography, chest computed tomography (CT) scan, cardiac catheterization, surgery, and pathological criteria. The most important diagnostic tool is the suspicion of constrictive pericarditis in a patient with signs and symptoms of right-sided heart failure that are disproportionate to pulmonary of left-sided heart disease. Typical symptoms and signs are a prominent change in the x and y descent in jugular venous pulse, dyspnea upon exertion, palpitations, abdominal distension, as well as edema in the ankles or legs. Echocardiography and chest computed tomography scan revealed a severely thickened or calcified pericardium, and cardiac catheterization revealed elevated end-diastolic pressure and the "square root sign" of right ventricular pressure tracing. A thickened pericardium of more than 4 mm on cardiac CT is supportive of the diagnosis and the best modality for the evaluation of pericardial calcification. Surgical and pathological findings were reviewed to confirm the preoperative diagnosis [Burak 2017]. (Figure 1)

Follow up: All survivors discharged from hospital were monitored to the end date of the study. At the outpatient department, all patients were investigated with echocardiogram, electrocardiogram, and X-ray chest film, once every 3

Table 7. Analysis of risk factors of low cardiac output syndrome after pericardiectomy

Model	OR	95%CI	*P*-value
Univariable analysis of risk factors of low cardiac output syndrome			
Male	2.917	1.018-1.033	<0.001
Weight before diuresis	0.967	0.947-0.987	0.001
Weight after diuresis	0.959	0.937-0.982	0.001
Height	0.913	0.891-0.935	<0.001
BMI before diuresis	1.059	0.999-1.122	0.055
BMI after diuresis	1.082	1.014-1.153	0.017
Time between symptoms and surgery	1.025	1.018-1.033	<0.001
Bleeding during operation	1.001	1.000-1.002	<0.001
Thickness of pericardium	1.088	1.051-1.125	<0.001
Intubation time	1.014	1.012-1.017	<0.001
ICU retention time	1.236	1.190-1.285	<0.001
Hospitalized time postoperative	1.042	1.027-1.058	<0.001
Preoperative CVP	1.240	1.190-1.293	<0.001
Postoperative CVP	1.177	1.109-1.249	<0.001
Preoperative LVEDD	0.898	0.860-0.937	<0.001
Postoperative LVEDD	0.690	0.622-0.766	<0.001
D0 fluid balance	1.001	1.001-1.002	<0.001
D2 fluid balance	0.999	0.999-0.999	<0.001
Chest drainage	1.002	1.001-1.002	<0.001
Serum creatinine 24h after surgery	1.040	1.032-1.049	<0.001
Serum creatinine 48h after surgery	1.046	1.038-1.053	<0.001
Fresh-frozen plasma	1.001	1.001-1.002	<0.001
Packed red cells	1.503	1.310-1.724	<0.001
Surgical duration	1.014	1.011-1.017	<0.001
Preoperative tricuspid regurgitation	0.961	0.887-1.040	0.324
Postoperative tricuspid regurgitation	0.995	0.881-1.123	0.929
Tuberculosis pericarditis	2.000	1.342-2.980	0.001
Blood lactate	1.898	1.722-2.093	<0.001
Multivariable analysis of risk factors of low cardiac output syndrome			
Postoperative LVEDD	0.630	0.545-0.728	<0.001
Female	186.0	37.9-913.4	<0.001
Weight before diuresis	1.192	1.002-1.417	0.047
Weight after diuresis	0.781	0.636-0.961	0.019
Intubation time	1.008	1.001-1.016	0.023
ICU retention time	1.876	1.555-2.263	<0.001
Hospitalized time postoperative	0.821	0.774-0.871	<0.001
D0 fluid balance	1.001	1.000-1.001	<0.001
D1 fluid balance	1.000	1.000-1.001	0.211
D2 fluid balance	0.999	0.999-1.000	<0.001
Chest drainage	1.002	1.001-1.003	<0.001
Preoperative LVEDD	0.836	0.773-0.904	<0.001

Pericardial calcification	0.208	0.082-0.529	0.001
Serum creatinine 24h after surgery	0.967	0.948-0.986	0.001
Serum creatinine 48h after surgery	1.090	1.068-1.113	<0.001
Fresh-frozen plasma	1.002	1.002-1.003	<0.001
Packed red cells	0.306	0.191-0.490	<0.001
Tuberculosis pericarditis	0.336	0.129-0.877	0.026
Surgical duration	1.010	1.004-1.016	0.001
Time between symptoms and surgery	1.017	1.002-1.033	0.030
Preoperative CVP	1.274	1.145-1.418	<0.001
Postoperative CVP	1.937	1.158-2.574	<0.001
Bleeding during operation	0.991	0.985-0.996	0.001
Thickness of pericardium	1.928	1.487-2.500	<0.001
Tuberculosis pericarditis	50.68	2.01-1277.8	0.017
Blood lactate	9.026	4.166-19.55	<0.001

to 12 months. At the last follow up, patients were contacted by telephone or micromassage or interviewed directly in the outpatient department.

Preoperative and operative data: Included in the study were 826 consecutive patients undergoing pericardiectomy for constrictive pericarditis. The patients were divided into two groups: group with LCOS ($N = 126$) and group without LCOS ($N = 700$) (Table 1 and Table 2). (Table 1)

Time between symptoms and surgery (23.3±4.3 vs. 6.7±0.7 months, $P < 0.001$), thickness of pericardium (22.7±0.6 vs. 19.7±0.3 mm, $P < 0.001$), preoperative CVP (25.1±0.0 vs. 19.2±0.2 mmHg, $P < 0.001$) in the group with LCOS were significantly higher than those in group without LCOS (Table 2).

Mortality: The incidence of postoperative LCOS in the study was 15.3% (126/826). There were 66 operative deaths (66/826, 8.0%). Mortality in the group with LCOS was significantly higher than in group without LCOS (52.4% vs. 0, $P < 0.001$).

Resource utilization: Intubation time and ICU retention time of the group with LCOS were significantly longer than those of group without LCOS (149.2±12.3 h vs. 56.4±2.7 h, $P < 0.001$; 12.7±1.3 d vs. 4.5±0.1 d, $P < 0.001$, respectively). (Table 3) One patient required extracorporeal membrane oxygenation.

Postoperative LVEDD of the group with LCOS was significantly smaller than that in the group without LCOS (40.2±0.4 mm vs. 43.9±0.2 mm, $P < 0.001$). Fluid balance on operation day (D0) of the group with LCOS were significantly less negative than in the group without LCOS (-647.6±61.0 ml vs. -1214.2±40.5 ml, $P < 0.001$). Fluid balance on postoperative day D2 of the group with LCOS was significantly more negative than that of the group without LCOS (-1140.0±153.3 ml vs. -468.4±26.0 ml, $P < 0.001$). Use of adrenaline of the group with LCOS were significantly higher than that of the group without LCOS (100% vs. 19.9%, $P < 0.001$; 1.8±0.03 vs. 0.02±0.01 μg/kg/min, $P < 0.001$, respectively) (Table 3).

Bleeding during operation (516.7±29.1 vs. 388.0±15.4ml, $P < 0.001$), chest drainage (1331.0±88.5 vs. 766.7±21.7 ml, $P < 0.001$), and surgical duration (230.4±6.6 vs. 174.4±2.7 mins, $P < 0.001$) of the group with LCOS were significantly more than those of the group without LCOS.

Table 4 showed the use of inotropic medication ($N = 826$). (Table 4)

Postoperatively, CVP decreased statistically significantly ($P < 0.001$), and LVEDD and LVEF improved statistically significantly ($P < 0.001$ and $P < 0.001$, respectively. (Table 5)

The common early postoperative complications included acute renal injury (222/826, 26.9%), long-term intubation time >48h (393/826, 47.6%), and multiorgan failure (86/826, 10.4%). (Table 6)

Analysis of risk factors of low cardiac output syndrome after pericardiectomy: Univariable analysis of potential risk factors of LCOS showed that numerous factors are associated with LCOS, including male ($P < 0.001$), postoperative LVEDD ($P < 0.001$), preoperative LVEDD ($P < 0.001$), time between symptoms and surgery ($P < 0.001$), thickness of the pericardium ($P < 0.001$), intubation time ($P < 0.001$), ICU retention time ($P < 0.001$), postoperative hospitalization time ($P < 0.001$), preoperative central venous pressure ($P < 0.001$), postoperative central venous pressure ($P < 0.001$), D0 fluid balance ($P < 0.001$), D2 fluid balance ($P < 0.001$), postoperative chest drainage ($P < 0.001$), surgical duration ($P < 0.001$), bleeding during operation ($P = 0.001$), serum creatinine 24h after surgery ($P < 0.001$), serum creatinine 48h after surgery ($P < 0.001$), fresh-frozen plasma ($P < 0.001$), and packed red cells ($P < 0.001$).

When they were included in multivariate analysis models, multivariable analyses also showed that numerous factors are associated with LCOS, including postoperative LVEDD ($P < 0.001$), preoperative LVEDD ($P < 0.001$), time between symptoms and surgery ($P < 0.001$), thickness of the pericardium ($P < 0.001$), intubation time ($P = 0.002$), postoperative hospitalization time ($P < 0.001$), preoperative central venous pressure ($P = 0.016$), postoperative central venous pressure ($P = 0.034$), D0 fluid balance ($P = 0.019$), D2 fluid balance ($P = 0.017$), postoperative chest drainage ($P < 0.001$), surgical duration ($P < 0.001$), bleeding during operation ($P = 0.001$), serum creatinine 24h after surgery (P < 0.001), serum creatinine 48h after surgery (P = 0.017), fresh-frozen plasma (P = 0.005), packed red cells (P = 0.006), and tuberculosis pericarditis (P = 0.026) (Table 7).

Histopathologic study results: Histopathologic studies of pericardium tissue from every patient were done. The diagnosis of tuberculosis was confirmed on clinical findings and histopathologic features, including the presence of typical granuloma and caseous necrosis, acid-fast bacilli in Ziel-Nelson tissue staining, and bacteriologic studies using the polymerase chain reaction (PCR) test on the pericardial fluid or tissue for evidence of mycobacterium tuberculosis.

In this series from Guangxi, China, characteristic histopathologic features of tuberculosis (434/826, 52.5%) of the pericardium were the most common histopathologic findings, and 260 patients (392/826, 47.5%) had the histopathologic findings of chronic nonspecific inflammatory changes. (Figure 2)

Follow-up results: There were 760 survivors discharged from the hospital, and 684 patients were monitored to the end date of the study. Follow up was 90.0% (684/760) completed. The mean duration of follow up was 126.4 ± 3.5 months (range, 1 to 342), seven late deaths (7/684, 1.0%) occurred 131, 193, 208, 210, 215, 240, and 300 months after being discharged from our hospital. Three patients died of heart failure, one of cerebral hemorrhage, and three of unknown reasons. The latest data of follow up showed that 656 survivors were in NYHA class I (656/684, 95.9%) and 21 in class II (21/684, 3.1%). (Figure 3)

DISCUSSION

LCOS is major problem after pericardiectomy, increasing mortality, morbidity, and hospital stay. Surgical removal of the pericardium is associated with an operative mortality rate of 5% to 20% in various large series [Bhattad 2020]. In our study, the incidence of postoperative LCOS in the study was 15.3% (126/826). There were 66 operative deaths (66/826, 8.0%). Mortality in the group with LCOS was significantly higher than in the group without LCOS (52.4% vs. 0, P < 0.001) (Table 3). Because of a decreased ejection fraction and decreased oxygen supply, LCOS may cause hypoxia. The patients with LCOS often are at high risk of mortality and need more intensive care, such as prolonged stay in the intensive care unit and ventilatory support [Rupprecht 2018]. In our study, intubation time and ICU retention time of the group with LCOS were significantly longer than those of the group without LCOS (149.2±12.3 h vs. 56.4±2.7 h, P < 0.001; 12.7±1.3 d vs. 4.5±0.1 d, P < 0.001; respectively) (Table 3). Determining the risk factors of LCOS has clinical significance for the management of pericardiectomy.

The etiology of low cardiac output syndrome following pericardiectomy: The pathophysiology of LCOS is not clear but seems to be related with sudden hemodynamic changes after myocardial decompression following pericardiectomy. It is speculated that etiology, myocardial atrophy, long time between symptoms and pericardiectomy, and concomitant myocardial disease are factors that may contribute to LCOS. The residual hemodynamic burden of residual constriction can lead to LCOS following pericardiectomy [Epting 2016; McCaughan 1985; Ling 1999]. Thus, a study aimed at clarifying this knowledge gap is highly desired. In our study, time between symptoms and surgery (23.3±4.3 vs. 6.7±0.7 months, P < 0.001), thickness of the pericardium (22.7±0.6 vs. 19.7±0.3 mm, P < 0.001), and preoperative CVP (25.1±0.0 vs. 19.2±0.2 mmHg, P < 0.001) in the group with LCOS were significantly higher than those in group without LCOS (Table 2).

Univariable and multivariable analyses showed that factors, including time between symptoms and surgery (P < 0.001), thickness of pericardium (P < 0.001), preoperative LVEDD (P < 0.001), preoperative CVP (P < 0.001), intubation time (P < 0.001), and ICU retention time (P < 0.001) are associated with LCOS (Table 7).

Incomplete pericardial dissection is associated with low cardiac output syndrome following pericardiectomy. The causes of low cardiac output syndrome are related to the incomplete resection of thickened pericardium, unsatisfactory relief of left ventricular compression, excessive ventricular dilatation after pericardial dissection, myocardial weakness, and heart failure. The relief of left heart compression is very important for the recovery of cardiac function after operation. The apical adhesions should be free enough to restore the rotation function of normal ventricular contractions [Gatii 2020; Chandler 2016]. In our study, postoperative LVEDD of the group with LCOS was significantly smaller (not larger) than that in the group without LCOS (40.2±0.4 mm vs. 43.9±0.2 mm, P < 0.001), and univariable and multivariable analyses showed that postoperative LVEDD (P < 0.001) is associated with LCOS (Table 7). We hypothesize that the incomplete resection of thickened pericardium and unsatisfactory relief

A SUPPLEMENTAL

Variables were evaluated, including gender (female/male), age, weight before diuresis, weight after diuresis, time between symptoms and surgery, thickness of pericardium, NYHA class, cachexia, pulmonary tuberculosis, rheumatic heart disease, infective endocarditis, valvular heart disease, coronary heart disease, pleural effusion, left ventricular end diastolic dimension, left ventricular ejection fractions, aortic insufficiency, mitral regurgitation, tricuspid regurgitation, thickened pericardium, pericardial effusion, pericardial calcification, serum creatinine, mean intubation time, ICU retention time, hospitalized time after surgery, central venous pressure, postoperative chest drainage, surgical duration, bleeding during operation, fresh-frozen plasma, packed red cells, fluid balance on operation day, the first day following operation and the second day following operation, low cardiac output syndrome, acute renal injury, multiorgan failure, long-term intubation, empyema, hepatic failure, respiratory failure, ventricular fibrillation, use of inotropic medication, blood lactate, extracorporeal membrane oxygenation (ECMO) requirement, and death.

of left ventricular compression are associated with LCOS following pericardiectomy.

We reported a relatively high incidence of postoperative LCOS of 15.3% (126/826). We removed the pericardium from phrenic nerve to phrenic nerve without CPB as the procedure of choice. However, this often results in insufficient removal of pericardium to relieve the constriction, especially in cases of complete encirclement of the heart, most frequently around the base by a heavily thickened calcified ring (Figure 2). In these situations, the postero-lateral and inferior wall pericardial thickening that sometimes are associated with severe cardiac compression are left behind. Therefore, in severe constrictive pericarditis as these, the textbook approach of phrenic nerve to phrenic nerve removal often will be not nearly enough to relieve the constriction. It is perhaps for this reason that there was such a high percentage of patients experiencing LCOS after pericardiectomy.

Without CPB, severe circumferential pericardial constriction often cannot be effectively removed. In instances of heavy myocardial infiltration of calcification, these lesions cannot be safely and effectively removed without CPB with or without left ventricle venting. Therefore, CPB actually is a vital maneuver if the primary aim is to achieve complete relief of the constriction. In our report, only patients requiring concomitant cardiac procedures underwent CPB. However, full institution of CPB for the reasons stated should be the routine rather than the exception. The brief additional CPB time during the procedure adds very little to the morbidity risk of the main surgery [Chang 2019; Fang 2020]. Median sternotomy provides more radical removal of the pericardium over the right atrium and venae cavae and allows extensive pericardial removal by using cardiopulmonary bypass. Cardiopulmonary bypass aids in surgical dissection by emptying the ventricular cavities to clearly define the appropriate plane of dissection and facilitates the management of inadvertent cardiac injury. Therefore, complete pericardiectomy (phrenic to phrenic removal and removal of the postero-lateral and inferior wall pericardial thickening) on CPB for complete relief of the constriction of the heart should be the routine.

Bleeding during operation (516.7±29.1 vs. 388.0±15.4ml, $P < 0.001$), chest drainage (1331.0±88.5 vs. 766.7±21.7 ml, $P < 0.001$), and surgical duration (230.4±6.6 vs. 174.4±2.7 mins, $P < 0.001$) of the group with LCOS were significantly more than those of the group without LCOS. Univariable and multivariable analyses showed that bleeding during operation, chest drainage, and surgical duration are associated with LCOS ($P < 0.001$) (Table 7). Improvement of surgical techniques can decrease bleeding during operation, chest drainage, and surgical duration.

Fluid balance on operation day and fluid balance postoperative day D2 are associated with low cardiac output syndrome following pericardiectomy. During the process of pericardial dissection, acute low cardiac output syndrome may occur, due to acute cardiac dilatation, especially after the pericardium was removed from the surface of right ventricle. Because of systemic venous hypertension, the ventricle rapidly fills and expands, therefore, fluid input should be limited during the operation. Inotropes and furosemide should immediately be applied after the left ventricular constriction is relieved. Dopamine and other catecholamines should be used. If the drug response is poor and the low cardiac output syndrome cannot be corrected, extracorporeal membrane oxygenation should be used [Vondran 2019; Ahmad 2019]. The volume and speed of fluid input should strictly be controlled to avoid sudden increase of heart burden to cause acute heart failure and pulmonary edema. Blood transfusion and plasma or albumin should appropriately be applied for patients with anemia or low serum protein. In our study, fluid balance on operation day (D0) of the group with LCOS was significantly less negative than that of the group without LCOS (-647.6±61.0 ml vs. -1214.2±40.5 ml, $P < 0.001$). While fluid balance postoperative day D2 of the group with LCOS was significantly more negative than that of the group without LCOS (-1140.0±153.3 ml vs. -468.4±26.0 ml, $P < 0.001$). Univariable and multivariable analyses showed that fluid balance on operation day and fluid balance postoperative day D2 are associated with LCOS ($P < 0.001$) (Table 7).

Patients following pericardiectomy for constrictive pericarditis hospitalized in the ICU are constantly subjected to volume overload. In addition to the fluids received during the resuscitation phase, these patients receive a volume related to medications and nutrition, which easily promotes overload. Therefore, in this maintenance phase, it is important to minimize, or even avoid, the administration of non-essential fluids. Once fluid overload is identified in patients with greater hemodynamic stability and reductions in vasopressors and mechanical ventilation parameters, the removal of excess volume should become a target, promoting a negative water balance as soon as possible within 48 hours postoperatively. The control and optimization of fluid balance is a key element of management of patients following pericardiectomy, since inadequate fluid removal is associated with peripheral edema and pulmonary edema. During fluid administration, cardiac function needs to be closely monitored either with echocardiography or with cardiac output monitoring [Bagshaw 2010; Walker 2015].

Interventions for low cardiac output syndrome: The initiation of therapeutic strategies, such as inotropes, steroids, inodilators, afterload reducing agents, and mechanical ventilation, may all have a role in augmenting cardiac output, decreasing oxygen demand and improving the relationship between oxygen supply and demand. When medical interventions fail, transition to extracorporeal support should be pursued to support end organ function, allowing for myocardial recovery [Chandler 2016].

Patient selection and timing of pericardiectomy: Pericardiectomy is indicated once the diagnosis of constrictive pericarditis is made. Systematic antituberculosis drugs should be given to patients with constrictive pericarditis caused by tuberculous bacteria. Surgery should be performed after body temperature, erythrocyte sedimentation rate, and general nutritional status are normal or relatively stable and before cardiogenic cachexia and severe live function injury occur. In our study, time between symptoms and surgery (23.3±4.3 vs. 6.7±0.7 month, $P < 0.001$) , thickness of pericardium (22.7±0.6 vs. 19.7±0.3 mm, $P < 0.001$), and preoperative CVP (25.1±0.0

vs. 19.2±0.2 mmHg, $P < 0.001$) in the group with LCOS were significantly higher than those in group without LCOS (Table 2). Univariate and multivariate analyses showed that factors, including time between symptoms and surgery ($P = 0.030$), thickness of pericardium ($P < 0.001$), and preoperative CVP ($P < 0.001$) are associated with LCOS (Table 7). Therefore, early diagnosis and treatment of constrictive pericarditis are important. Early surgical intervention is advocated, as constrictive pericarditis is a progressive disease, and patients with a poor preoperative functional class are at the highest risk for perioperative death [Bhattad 2020; Unai 2019].

Histopathologic study results: In this series from Guangxi, China, tuberculosis (434/826, 52.5%) is the major cause of constrictive pericarditis (Figure 3, Figure 4). (Figure 4) At present, idiopathic or viral pericarditis is the predominant cause of constrictive pericarditis in the Western world, followed by post-cardiotomy irritation and mediastinal irradiation [Gatti 2020; Maisch 2004]. In our study, tuberculosis pericarditis of the group with LCOS were significantly more than that of the group without LCOS (69.0% vs. 49.9%, $P < 0.001$). Univariable and multivariable analyses showed that tuberculosis pericarditis is associated with LCOS ($P = 0.001$ and $P = 0.017$, respectively) (Table 7).

In conclusion, CPB is actually a vital maneuver to achieve complete relief of the constriction. In this report, only patients requiring concomitant cardiac procedures underwent CPB. The brief additional CPB time during the procedure adds very little to the morbidity risk of the main surgery. It is perhaps incomplete pericardiectomy that was the cause of postoperative remnant constriction and high diastolic filling pressure which eventually led to multiorgan failure.

Study limitations: Limitations of the present study include its retrospective design. There may be a selection bias because of the retrospective nature of the study.

CONCLUSION

In our study, incomplete pericardial dissection, fluid overload, delayed diagnosis and treatment, and tuberculosis pericarditis are associated with low cardiac output syndrome following pericardiectomy. A study looking at the outcomes of the procedures with routine CPB would be helpful.

ACKNOWLEDGEMENT

This work was supported by the Natural Science Foundation of China (No: 81360014), Natural Science Foundation of Guangxi (No: 2014GXNSFAA118234), Guangxi key scientific and technological project (No: 2013BC26236), and Projects in Guangxi Health Department (No: GZPT13-27).

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