Published in final edited form as:

Am J Cardiol. 2014 November 1; 114(9): 1426–1430. doi:10.1016/j.amjcard.2014.07.078.

Clinical Features Associated with Adverse Events in Patients with Post-Pericardiotomy Syndrome Following Cardiac Surgery

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Abstract

Post-pericardiotomy syndrome (PPS) maybe associated with tamponade and pericardial constriction that may require procedural intervention. We sought to identify clinical features associated with adverse events requiring procedural intervention in patients with PPS. We monitored 239 patients who developed PPS after cardiac surgery for 12 months. PPS was diagnosed if 2 of the 5 following findings were present: fever without infection, pleuritic pain, friction rub, pleural effusion, and/or pericardial effusion (within 60 days post-surgery). Primary endpoint was the development of pericardial effusion or pericardial constriction requiring procedural intervention. Among 239 patients with PPS, 75 (31%) required procedural intervention. In a univariate analysis, the odds of a procedural intervention were decreased with older age (OR 0.98, 95% CI 0.96-0.99) and with colchicine used in combination with anti-inflammatory agents (OR 0.45, 95% CI 0.26-0.79). However, the odds were increased in patients with preoperative heart failure (OR 1.84, 95% CI 1-3.39) and early postoperative constrictive physiology (OR 5.77, 95% CI 2.62-12.7). After multivariable adjustment, treatment with colchicine along with anti-inflammatory agents was associated with lower odds of requiring intervention (OR 0.43, 95% CI 0.95-0.99). Independent positive predictors of procedural intervention included age (OR 0.97, 95% CI 0.95-0.99), time to PPS (OR 0.97, 95% CI 0.95-0.99), and early postoperative constrictive physiology (OR 6.23, 95% CI 2.04-19.07). In conclusion, younger age, early onset PPS, and postoperative constrictive physiology were associated with the need for procedural intervention in patients with PPS; whereas, colchicine was associated with reduced odds of adverse events and procedural intervention.

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Disclosures: None

Keywords

pericarditis; post-pericardiotomy syndrome; pericardial effusion; tamponade; constrictive pericarditis

INTRODUCTION

Post-pericardiotomy syndrome (PPS) is an inflammatory process that develops in patients who have undergone surgery that involves opening the pericardium (1). PPS typically affects 10-40% of patients and occurs anywhere from a few days to few weeks after cardiac surgery (1). The severity of PPS can present as acute or recurrent pericarditis, pericardial effusion with or without tamponade, or constrictive pericarditis with hemodynamic instability requiring surgical intervention (2). Medical treatment consists of nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and in severe cases, oral steroids (3-6). PPS is diagnosed by the presence of at least 2 of the following clinical features: fever in the absence of infectious source; pleuritic chest pain; pericardial friction rub; pleural effusion; and a persistent pericardial effusion one to several weeks after surgery (3). Severe consequences associated with PPS, include large pericardial with cardiac tamponade or constrictive pericarditis, which require pericardiocentesis or pericardiectomy, respectively (4,7-8). Identification of clinical features that predict the need for procedural intervention in patients with PPS becomes important to initiate preventive therapy. In this observational study, we sought to examine clinical characteristics associated with a need for procedural interventions in PPS patients.

METHODS

From the Cleveland Clinic pericardial disease database, we retrospectively identified 239 consecutive patients diagnosed with PPS between 1/1/2007 and 12/31/2010 who met the following criteria: 1) age >18 years; 2) history of prior cardiac surgery including coronary artery bypass grafting (CABG), valvular repair or replacement, ascending aorta surgery; and 3) clinical diagnosis of PPS within 12 months following surgery. Electronic medical records were used to collect patients' demographics, laboratory and imaging data, medical and surgical treatments. Those who were lost to follow up were excluded from the study. Patients were considered to have PPS if they met 2 of the 5 following criteria: fever in the absence of an infectious source; pleuritic chest pain; friction rub; pleural effusion; and pericardial effusion of any size after surgery (3-4). The primary endpoint was a procedural intervention within 12 months post diagnosis of PPS. Procedural intervention was due to: hemodynamically significant pericardial effusion with tamponade requiring pericardiocentesis or pericardial window and/or constrictive pericarditis refractory to medical therapy and requiring pericardiectomy. Cardiac tamponade was defined as the presence of a moderate to large pericardial effusion with echocardiographic and clinical features of tamponade (9-10). Constrictive pericarditis was diagnosed by the presence of a constellation of clinical symptoms; evidence of right heart failure; and echocardiographic, hemodynamic and/or cardiac magnetic resonance (CMR) imaging-based criteria (10). Continuous variables were expressed as means $\pm$ standard deviation and categorical

variables as percentages. The unpaired Student t-test was used to compare continuous variables (normal distribution), and Fisher exact test or Chi-square test was used for categorical variables, as appropriate. The predictors of failed medical therapy post PPS response were investigated using multivariate logistic regression analysis. Variables that were significant on univariate analysis were entered into a multivariate model using a forward Wald selection to obtain the final model. The strength of the model was expressed using Nagelkerke R². All statistical tests were two sided. A p value <0.05 was set a priori and considered statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences, version 11.5, for Windows (SPSS, Chicago, Illinois).

RESULTS

Of 1082 consecutive patients in the pericardial disease database between 1/1/2007 and 12/31/2010, 843 patients did not meet inclusion criteria and were excluded (Figure 1). The study cohort consisted of 239 patients (mean age 58±16 years, 72% male) who developed PPS after a mean time of 27±18 days post cardiac surgery (Table 1). All patients who experienced PPS with cardiac surgery were followed for 12 months post diagnosis with PPS.

Among patients with PPS, procedural interventions were required in 31%. Of the diagnostic criteria used to define PPS, the most common findings in our patient cohort included pericardial effusion (88%); pleuritic chest pain (57%); and pleural effusion (56%). All patients with fever had a negative work up for an infectious etiology and were not treated with antibiotics. CABG was the most common surgery performed among patients included in this study (42%) followed by aortic valve surgery (29%) mitral valve surgery (26%) and aortic surgery (23%). PPS and its complications were independent of the type of surgery. Patients presented with PPS approximately 3-4 weeks after surgery. Treatment for PPS included NSAID (41%); ASA (75%); steroids (35%); colchicine (21%); and a combination of colchicine with another anti-inflammatory medication in 41% of patients. Inflammatory markers including C-reactive protein (CRP) and the Westergren sedimentation rate (WSR) were elevated among all patients after cardiac surgery. Overall, 14% of patients with PPS presented with constrictive physiology defined as symptoms of right heart failure along with echocardiographic findings of constriction within 2 weeks after surgery (11) (Figure 2). All patients with constrictive pericarditis (31 patients) had CMR imaging. Pathologic change in the pericardium defined as pericardial thickness>2mm was present in only 5 patients (16%) (Figure 2). Among the 239 patients who presented with PPS, 75 developed complications leading to procedural interventions. Pericardial effusion with tamponade was present in 44 patients and among them 20 underwent pericardiocentesis and 24 required pericardial window. Pericardial constriction refractory to therapy and requiring pericardiectomy was present in 31 patients (Figure 1). Patients with PPS who required procedural interventions were younger than those free of complications (Table 1). They also manifested clinical features of PPS earlier in the postoperative period compared to those who were free of complications.

In a univariate analysis, the odds of procedural interventions decreased with older age, odds ratio (OR) 0.98, 95% CI 0.96-0.99 and use of colchicine in addition to one or more anti-inflammatory medications for treatment OR 0.45, 95% CI 0.26-0.79 (Table 2). In contrast,

development of constrictive physiology in the immediate postoperative period increased the odds of procedural interventions with OR 5.77, 95% CI 2.62-12. Patients with congestive heart failure prior to surgery also had an increased odds of requiring post-surgical procedural intervention. In a multivariable binary regression analysis, independent predictors of procedural intervention were: younger age, early development of PPS, and pericardial constriction in the immediate postoperative period. In contrast, treatment with a combination of colchicine and anti-inflammatory medications was associated with reduced odds of adverse events and the need for procedural intervention (Table 2).

DISCUSSION

PPS, a postoperative complication after cardiac surgery, can be disabling and in some patients may be associated with adverse events that include tamponade or constrictive pericarditis. These complications may require procedural intervention such as pericardial window, pericardiocentesis or pericardiectomy. This is an observational study that describes the clinical characteristics seen in patients with PPS who require procedural intervention including pericardiocentesis or pericardial window for tamponade or pericardiectomy for constrictive pericarditis in the postoperative period. In this single center study of a large number of PPS patients, we showed for the first time that younger patients are more susceptible to adverse outcomes and that administration of colchicine along with other anti-inflammatory medications is associated with reduced risk of adverse outcomes.

PPS is an immune mediated inflammatory process that affects the pericardium in patients who have undergone cardiothoracic surgery. Although this syndrome has been described by a set of diagnostic clinical features, scarce data describe the incidence of these clinical criteria used to identify patients affected by PPS in a large post-surgical population. One of the largest single center studies published to date by Miller et al. examined 168 patients diagnosed with PPS (11). In that study, approximately 66% of patients presented with chest pain, while in our study population, new or worsening pericardial effusion was the most common symptom associated with PPS. In our study we found that among patients with PPS, procedural interventions were required in 31% which is a higher rate compared to the previously reported complication rate in Colchicine for the Prevention of the Post-Pericardiotomy Syndrome (COPPS) trial. This is most likely due to a selection bias and reflects the advanced disease in most patients referred for cardiothoracic surgery at the Cleveland Clinic. All of the PPS events occurred during the first month, which is consistent with findings in the COPPS trial, a prospective, multicenter, doubleblind, randomized trial for the primary prevention of PPS (4). Among patients who presented with PPS, the odds of complications requiring procedural intervention were increased in those who developed PPS early in the postoperative period. Similarly, the odds of requiring procedural intervention were higher when patients presented with features of pericardial constriction in the immediate postoperative period. It is likely that early development of PPS and postoperative pericardial constriction signal a heightened inflammatory response that increases the risk of further complications including severe constriction or tamponade. It is conceivable that in these individuals, early initiation of anti-inflammatory therapy may be beneficial in preventing adverse events. We observed that younger patients were more susceptible to PPS and the odds of requiring procedural intervention for PPS declined with increasing age.

Although no large studies have examined the risk factors leading to adverse events in PPS patients, an epidemiological study by Miller et al. showed that younger age was a significant independent risk factor for developing PPS (11). We hypothesize that a decline in immune response with advanced age may play a protective role in patients who develop PPS; and older patients may, therefore, experience less adverse outcomes when they develop PPS. PPS prevention may be crucial especially in the subset of cardiac surgery patients with increased risk of developing this condition. The COPPS study found that colchicine significantly reduced the incidence of PPS at 12 months compared with a placebo. Although, the administration of colchicine is a class I indication for recurrent pericarditis and class IIa indication for acute pericarditis, the use of colchicine for the prevention of PPS has been recommended but has not been formally adopted into official guidelines (4 and 9). We observed that among PPS patients, administration of colchicine along with NSAIDs or steroids was associated with lower odds of requiring procedural intervention. We acknowledge that our results do not point to a causal relationship between colchicine use and favorable outcomes in patients with PPS. Furthermore, our study was not designed to test the efficacy of colchicine in treating PPS or in preventing adverse events associated with PPS. A more targeted trial will be necessary to establish the benefit of colchicine in preventing adverse events in patients who develop PPS.

The diagnosis of PPS can be challenging, as there are no pathognomonic features of this condition. Furthermore, there is no consensus or specific guidelines defining PPS; however, we used criteria that have been widely adopted and used by other investigators including Imazio et al. in the COPPS trial (4). This is a retrospective observational study conducted with patients referred to a single tertiary-care referral center, which induces a selection bias. This study is descriptive and does not provide an algorithm for risk stratification of patients with PPS who are likely to experience adverse outcomes. Although patients included in our study were observed for 6 months following diagnosis of PPS, it is likely that adverse events may have presented at a later date in some patients, in which case the incidence of adverse events may be underestimated. PPS is associated with significant morbidity and mortality and has a major impact on hospital stay, readmission rate, and cost (12). Based on our study, younger patients and those with features of early pericardial constriction may be at higher risk for developing tamponade and clinically significant pericardial constriction. We observed that colchicine is associated with a reduced risk of adverse events in patients who develop PPS; however, the clinical benefit of colchicine in PPS needs to be validated in prospective randomized clinical trial.

Acknowledgments

Funding resource: Dr. Tamarappoo received grant support from the NIH, 5KL2TR000440-07 and the AHA, 11CRP5050015.

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Highlights

- Patients with post-pericardiotomy syndrome (PPS) may require procedural intervention.
- We identified risk factors for procedural intervention in patients with PPS.
- Young patients with PPS were at greater risk for requiring intervention.
- Pericardial constriction early after surgery increased the risk for intervention.
- Treatment with colchicine was associated with lower risk of intervention

Figure 1.
Selection of patients for retrospective analysis

Figure 2.

Patient with pericardial constriction; echocardiogram and MRI of a 58-year-old man who had CABG surgery 3 weeks prior and presenting with fever and pleuritic chest pain.

Panel A is a parasternal short axis view of an echocardiogram illustrating increased pericardial thickness (arrow). Panel B illustrates tissue Doppler images of the same patient showing increased medial mitral annulus early diastolic (e') velocity (arrows). The panel on the left shows the septal e' and the panel on the right shows the reduced lateral e' velocity. Panel C illustrates a SSFP cine cardiac MRI of the same patient with pericardial thickening (arrow).

Table 1

Baseline patient characteristics stratified by the occurrence of procedural interventions

Variable	All Patients (N=239)	Procedural Intervention		P
		Yes (N=75)	No (N=164)	
Age (years.)	58±16 (60 [*])	55±15 (51 [*])	60±16 (62 [*])	0.03
Men	173(72%)	55(73%)	118(68%)	0.5
White	194(81%)	61(81%)	133(81%)	0.9
Time to PPS post-surgery (days)	27±18 (26 [*])	24±19 (24 [*])	29±17 (28 [*])	0.05
Body Mass Index (kg/m ²)	28±6	28±6	28±6	1.0
Connective tissue disease	28(12%)	10(13%)	18(11%)	0.7
Hypertension	162(68%)	50(67%)	112(68%)	0.9
Diabetes mellitus	44(18%)	13(17%)	31(19%)	0.9
Coronary artery disease	103(43%)	27(36%)	76(46%)	0.2
Congestive heart failure	60(25%)	25(33%)	35(21%)	0.05
Chronic kidney disease	7(3%)	2(3%)	5(3%)	1.0
Valvular heart disease	156(65%)	47(63%)	109(67%)	0.6
Atrial fibrillation	55(23%)	20(27%)	35(21%)	0.4
Smoker	109(46%)	34(46%)	75(46%)	1.0
Preop pericardial effusion	27(11%)	8(11%)	19(12%)	1.0
Prior cardiac surgery	83(35%)	27(36%)	56(34%)	0.8
Diagnostic Criteria for PPS				
Fever	112(47%)	36(48%)	76(46%)	0.9
Pleuritic chest pain	137(57%)	38(51%)	99(60%)	0.2
Pericardial rub	49(21%)	22(29%)	27(17%)	0.03
Pleural effusion	97(41%)	33(44%)	64(39%)	0.5
New/worsening pericardial effusion	211(88%)	62(83%)	149(91%)	0.08
Number of diagnostic criteria	2.7±1.1	2.5±1.3	2.7±1.1	0.2
Inflammatory Markers				
C-Reactive Protein (mg/L)	10.0±9.2	10.3±8.6	9.8±9.5	0.7
Sedimentation Rate (mm/h)	41±24	41±23	42±25	0.8
Post-Surgical Complications				
NYHA III-IV	150(63%)	55(73%)	95(58%)	0.03
Size of pericardial effusion				<0.0001
Mild (1.0 cm)	75(31%)	20(27%)	55(33%)	
Moderate (1.0-2.0 cm)	87(37%)	7(9%)	80(49%)	
Large (>2.0 cm)	77(32%)	48(64%)	29(18%)	
Constrictive physiology	33(14%)	22(29%)	11(7%)	<0.0001
Medications Postop for PPS				
Ibuprofen)	98(41%)	24(32%)	74(45%)	0.09
Aspirin	179(75%)	52(70%)	127(77%)	0.3
Prednisone)	84(35%)	24(32%)	60(37%)	0.3
Colchicine	51(21%)	10(13%)	41(25%)	0.06

Variable	All Patients (N=239)	Procedural Intervention		P
		Yes (N=75)	No (N=164)	
2 medications (including colchicine)	98(41%)	24(32%)	74(45%)	0.07
Perioperative Anticoagulation				
Unfractionated Heparin	36 (15%)	11 (14.6%)	25(15.2%)	1.0
Coumadin	38 (15.8%)	10 (13.3%)	28 (14%)	0.56

* Median (range)

Table 2

Independent predictors of procedural intervention

Variable	Univariate		Multivariate R ² =0.25	
	Odds ratio [95% CI]	P	Odds ratio [95% CI]	P
Age	0.98[0.96;0.99]	0.034	0.97[0.95;0.99]	0.018
Prior pericardial disease	2.3[0.80;6.8]	0.1		
Time to PPS	0.98[0.97;1.0]	0.053	0.97[0.95;0.99]	0.011
Congestive heart failure pre	1.84[1.003;3.39]	0.049	2.26[0.99;5.63]	0.053
Constriction post-op	5.77[2.62;12.7]	<0.0001	6.23[2.04;19.1]	0.001
Colchicine + one or more anti-inflammatory medication	0.45[0.26;0.79]	0.005	0.43[0.20;0.90]	0.025
Western sedimentation rate (mm/hr)	0.99[0.98;1.01]	0.8		

R²=0.25