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Original Article

# Pericardial effusion in prosthetic and native valve infective endocarditis

Ghada S. Youssef*, Marwa S. Mashaal, Dalia R. El Remisy, Khalid A. Sorour, Hussein H. Rizk

*Cardiology Department, Faculty of Medicine, Cairo University, Cairo 11411, Egypt*

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ABSTRACT

*Background:* Pericardial effusion (PE) is widely believed to signify more advanced infective endocarditis (IE) and a generally worse outcome.
*Purpose:* To determine the prevalence and clinical significance of PE in a series of patients with confirmed native and prosthetic valve infections.
*Methods:* Data were collected from 338 consecutive patients with definite or possible IE who visited a single referral center; these patients were examined for the presence of PE as detected by transthoracic echocardiography. Clinical characteristics, the incidence of complications, and outcomes were compared between patients with IE with and without PE. IE patients with PE were then divided into two subgroups: those with and those without cardiac prostheses.
*Results:* Eighty-eight patients out of the total 338 (26%) were found to have PE. Compared with patients who did not have PE, patients who did were significantly younger (32.9 ± 13.4 vs 29.0 ± 9.2, $p = 0.003$), had more left-sided vegetation (55.6% vs 77.3%, $p < 0.001$), more root abscesses (9.2% vs 25.0%, $p < 0.001$), needed surgery more frequently (68.0% vs 84.1%, $p = 0.001$), and had a higher mortality rate (22.0% vs 32.9%, $p = 0.03$). PE was not found to be a predictor of mortality. No significant difference was found between IE patients with PE with ($n = 13$) and without ($n = 75$) prostheses with regard to causative organisms, clinical characteristics, or clinical outcomes.
*Conclusion:* Regardless of whether the IE was in native or prosthetic valves, compared with patients without PE, patients with PE had more severe infections and a worse prognosis, but PE was not an independent predictor of mortality.


## 1. Introduction

It is not uncommon for pericardial effusion (PE) to occur in patients with infective endocarditis (IE), and an even higher prevalence of pericardial involvement was found when examining pathological specimens of the pericardium.[1] When IE is complicated by PE, an abscess should be suspected; transesophageal echocardiography should be immediately performed.[2] Many other mechanisms may cause PE in IE patients, including heart failure, renal failure, or sepsis (continuous bacteremia with pericardial seeding).[1] This study is aimed to define the prevalence of PE in patients with IE and to describe the clinical characteristics and outcomes of patients with PE complicating IE in native and prosthetic valves.

## 2. Methods

### 2.1. Study design

This was an observational, non-randomized study, and patients were recruited both prospectively and retrospectively (data collected from the IE registry).

Our university registry of patients with IE was established in 2005, and the recruitment of patients continued until 2017. The diagnosis of endocarditis was based on the modified Duke criteria.[3] All patients with definite or suspected endocarditis were included, except those who have undergone cardiac surgery within 3 months prior to IE diagnosis. The data collected include demographics, the history of contact with healthcare providers, the history of any procedure 3 months prior to the development of the infection, the use of antibiotic prophylaxis before a procedure, the location of vegetations according to echocardiography, the presence or absence of a cardiac prosthesis, the results of microbiological tests, the presence of

* Corresponding author.
*E-mail address:* ghadayoussef@kasralainy.edu.eg (G.S. Youssef).

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**The significance of the study**

- What is already known about this subject?

It is already known that the presence of pericardial effusion (PE) is not uncommon in infective endocarditis (IE) patients and that its presence is linked to the occurrence of root abscesses.

- What does this study add?

This study evaluates the impact of the presence of PE on patients with native valve IE versus patients with prosthetic valve IE. This comparison has never been made before.

- How might this impact clinical practice?

The findings of this study will guide physicians when managing IE patients with PE.

complications (heart failure, embolic complications, or fulminant sepsis), and mortality. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host to infection, according to the Third International Consensus definition.[4]

All the patients underwent transthoracic echocardiography, with or without transesophageal echocardiography, multiple times during the course of the illness. Echocardiography was performed using commercially available machines (PHILIPS Epiq-7), with a 2.5 MHz phased array transducer used for transthoracic views and an X7-2t xMATRIX Live 3D transducer used for transesophageal images. Patients who were found to have PE, regardless of the severity or time point during hospitalization, were included in the study.

As the fastest and the most accurate diagnostic tool, echocardiography was the standard procedure used in this study to detect the presence of PE.[5] PE is defined as the persistence of an echo-free space between the epicardial and parietal pericardium throughout the cardiac cycle.[6] Two-dimensional (2D) echocardiography allowed the proper assessment of the size and distribution of the PE.[5] Based on the results of 2D echocardiography, PE was semi-quantitatively described according to the size of the echo-free space observed between the parietal and visceral pericardium at the end of diastole as follows: trivial (seen only in systole), mild (<10 mm), moderate (10–20 mm), large (>20 mm), or very large (>25 mm).[5,7] PE was considered substantial if the echo-free space was >10 mm (moderate, large, and extreme PE). Cardiac tamponade was diagnosed when PE was associated with a dilated inferior vena cava and dilated hepatic veins, indicating an elevated systemic venous pressure; a right heart diastolic chamber collapse; an inspiratory bounce of the interventricular septum into the left ventricle; and characteristic abnormal respiratory changes on Doppler flow velocity recordings.[5]

Patients received standard care for IE and were followed into the hospital until discharge or death. Data about the progression of the disease and the occurrence of complications were systematically reported and documented. Patients who required surgical intervention were followed post-operatively by our IE team until discharge or death.

Patients with PE were classified into the following two subgroups: those with IE in prosthetic valves and those with IE in native valves. Clinical characteristics and hospital outcomes were compared between these two subgroups. As PE is a common post-operative finding, patients with IE in prosthetic valves in the immediate post-operative period were not included in the study; at least 3 months were required to pass before the presence of PE could be considered an abnormal finding.

### 2.2. Ethical issues

This study was approved by the institutional ethics committee and was performed in accordance with the ethical standards set by the 1964 Declaration of Helsinki and its later amendments.

### 2.3. Statistical analysis

Continuous variables are presented as the means and standard deviations, while categorical variables are presented as frequencies and percentages. Means were compared with Student's *t*-tests. Categorical variables were compared using Chi-squared and Fisher's exact tests. A multivariate analysis was performed using logistic regression analysis with mortality as the dependent factor. The $p$ values <0.05 were considered significant. All data analyses were performed with SPSS, version 20.

## 3. Results

By 2017, the university registry included 338 patients with native and prosthetic valve endocarditis and patients with cardiac electronic device-related endocarditis. Eighty-eight patients (26%) were found to have PE with differing levels of severity; 75/88 (85.2%) patients had mild PE, and 13/88 (14.8%) had substantial PE. None of the patients had cardiac tamponade. The baseline clinical characteristics and outcomes are shown in (Table 1). Patients with PE and IE were younger, had a higher incidence of left-sided vegetations and root abscesses, had a marginally higher incidence of sepsis, and a significantly higher incidence of splenic infarcts and splenic abscesses than patients without PE. It is worth noting that all PE patients with splenic abscesses ($n = 8$) had undergone successful ultrasound guided aspiration. Compared with patients without PE, patients with PE also had a greater need for cardiac surgery (because of the higher incidence of root abscesses) and a higher overall in-hospital mortality. The types of causative organisms were similar in patients with and without PE.

Patients with substantial PE (≥moderate effusion) had comparable outcomes to patients with mild PE (Fig. 1), in regard to the presence of root abscesses, the development of advanced heart failure, the need for dialysis, the occurrence of fulminant sepsis, and the overall mortality.

Among the patients with PE ($n = 88$), 13 (14.8%) patients had implanted prosthetic material, nine (69.2%) of whom had mitral valve replacement (MVR), three (23.1%) of whom had aortic valve replacement, and one of whom had a pacemaker device. The remaining 75 (85.2%) patients had native valve endocarditis.

The characteristics of patients with implanted prosthetic material and PE are shown in (Table 2). Compared with patients without prostheses, patients with prostheses' IE and PE had a higher incidence of having undergone procedures within the 3 months prior to the onset of infection and, accordingly, had received more prophylactic antibiotics before those procedures. Compared with patients with native valve endocarditis and PE, patients with prosthetic endocarditis and PE had significantly lower ejection fractions (EFs). It is worth noting that both groups had within normal EFs. No difference was found between the two groups regarding age, gender, causative organisms, size of vegetations, or basic laboratory data.

The complications of IE and the outcomes for patients are represented in (Table 3). The incidence of heart failure was similar among both groups. The heart failure was mainly caused by

**Table 1**
Baseline clinical characteristics and outcome of patients with (and without) pericardial effusion.

| Variable | Patients with PE ($n = 88$), No. (%) | Patients without PE ($n = 250$), No. (%) | $p$ value |
|---|---|---|---|
| Gender, male | 50 (56.8) | 155 (62.0) | 0.4 |
| Age (mean ± SD); years | 29.0 ± 9.2 | 32.9 ± 13.4 | 0.003 |
| Median (range); years | 28 (11 → 59) | 30 (3 → 75) | 0.024 |
| Healthcare-associated endocarditis | 10 (11.4) | 45 (18.0) | 0.1 |
| Presence of prosthetic valve or device ($n = 90$) | 13 (14.8) | 77 (30.8) | 0.003 |
| Renal impairment (creatinine >2.0 mg/dl) | 20 (22.7) | 53 (21.2) | 0.9 |
| **Causative organism** | | | |
| *Streptococcus viridans* | 7 (8.0) | 26 (10.4) | 0.4 |
| *Streptococcus pneumoniae* | 0 (0) | 2 (0.8) | 0.5 |
| *Enterococcus* | 4 (4.5) | 11 (4.4) | 0.6 |
| *Staphylococcus* spp.[a] | 23 (26.1) | 65 (26.0) | 0.7 |
| *Klebsiella* | 0 (0) | 2 (0.8) | 0.5 |
| *Pseudomonas* | 1 (1.1) | 4 (1.6) | 0.6 |
| HACEK group | 0 (0) | 2 (0.8) | 0.5 |
| Brucella | 4 (4.5) | 6 (2.4) | 0.3 |
| Others | 9 (10.2) | 2 (0.8) | |
| Culture negative | 40 (45.5) | 130 (52.0) | 0.4 |
| Fungal infection | 8 (9.0) | 16 (6.4) | 0.4 |
| Symptoms duration before presentation (days), **median (range)** | 21 (1 → 449) | 28 (1 → 730) | 0.72 |
| **Transthoracic echocardiography** | | | |
| Vegetation | 83 (94.3) | 175 (70.0) | <0.001 |
| Left-sided vegetation | 68 (77.3) | 139 (55.6) | <0.001 |
| Right-sided vegetation | 15 (17.0) | 38 (15.2) | 0.551 |
| Root abscess | 22 (25.0) | 23 (9.2) | <0.001 |
| Left-sided vegetation + root abscess | 16 (18.2) | 17 (6.8) | 0.012 |
| Tricuspid valve vegetation | 15 (17.0) | 36 (14.4) | 0.68 |
| Tricuspid valve regurgitation | 33 (37.5) | 82 (32.8) | 0.31 |
| **Overall complications** | 69 (78.4) | 181 (72.4) | 0.15 |
| Congestive heart failure | 41 (46.6) | 91 (36.4) | 0.26 |
| Sepsis requiring vasopressors | 15 (17.0) | 21 (8.4) | 0.049 |
| Splenic infarcts | 14 (15.9) | 14 (5.6) | 0.006 |
| Splenic abscesses | 8 (9.1) | 5 (2.0) | 0.006 |
| Indication for surgery[b] | 74 (84.1) | 170 (68.0) | 0.001 |
| Surgery performed | | | |
| Overall mortality[c] | 31 (35.2) | 54 (21.6) | 0.01 |

ESC, European Society of Cardiology; HACEK, Hemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella; PE, pericardial effusion; SD, standard deviation.
[a] Species.
[b] According to the ESC guidelines.[8]
[c] Overall mortality is any mortality throughout the course of endocarditis treatment during the patient's stay in hospital.

valvular lesions rather than reduced EFs. Patients with prosthetic IE and PE showed lesser response to antibiotics as compared with patients with native IE and PE, yet the difference was not statistically significant. Proper response to antibiotics is defined as clinical (disappearance of fever, improvement of appetite) and laboratory (reduction of inflammatory markers level; C-reactive protein level) improvement within 10 days of the initiation of antibiotics. Other clinical characteristics, complications, and outcomes were compared between patients with PE and either native or prosthetic endocarditis.

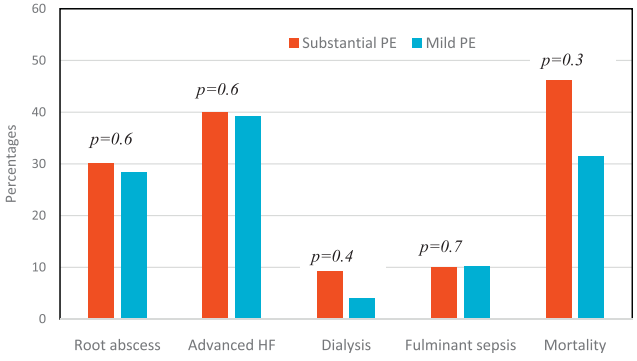


**Fig. 1.** Endocarditis complications in mild and substantial pericardial effusion. HF, heart failure; PE, pericardial effusion.

A multivariate logistic regression analysis was performed with the data from all IE patients, and the most significant predictors of mortality were sepsis [odds ratio (OR) = 42.2, 95% confidence interval (CI) = 5.5–325.7, $p < 0.001$] and intracranial hemorrhage (OR = 2.9, 95% CI = 1.2–7.3, $p = 0.03$). The presence of PE was not a predictor of mortality (OR = 1.97, 95% CI = 1.6–3.4, $p = 0.08$).

## 4. Discussion

The association between PE and IE is well known.[9] In this study, a quarter of IE patients had different grades of PE within the course of IE. Patients with PE were younger and had a higher incidence of left-sided vegetations and root abscesses than patients without PE. A relatively recent study conducted by Regueiro et al[1] evaluated the risk factors for PE in patients with native valve endocarditis. Data regarding the outcomes of patients with prosthetic IE associated with PE are lacking. Therefore, in this study, we studied both native and prosthetic endocarditis and investigated the prevalence of PE, clinical characteristics, and outcomes.

When IE is complicated by PE, abscesses should be suspected.[2] In this study, we demonstrated that approximately one-quarter of the patients who had PE also had abscesses, and patients with prosthetic valves had a numerically (but not statistically) higher incidence of abscesses than patients without prosthetic valves.

Regueiro et al[1] found that renal failure and younger age are two factors associated with a higher risk of PE in IE patients. In our

**Table 2**
Characteristics of patients with pericardial effusion with and without prosthetic material.

| Variable | PE and prosthesis IE ($n = 13$), No. (%) | PE and native valve IE ($n = 75$), No. (%) | $p$ value |
|---|---|---|---|
| Male gender | 9 (69.2) | 41 (54.7) | 0.3 |
| Age (years), (mean ± SD) | 32.2 ± 10.9 | 28.4 ± 8.9 | 0.2 |
| Previous use of antibiotics for the current fever before presentation | 7 (53.8) | 45 (60.0) | 0.3 |
| Any procedure within 3 months before presentation | 9 (69.2) | 17 (22.7) | 0.003 |
| Antibiotic cover before procedure | 6 (46.1) | 5 (6.7) | 0.001 |
| **Organism** | | | |
| *Staphylococcus* spp.[a] | 3 (23.1) | 20 (26.7) | 0.6 |
| Fungal infection | 3 (23.1) | 5 (6.7) | 0.09 |
| **Echocardiographic data** | | | |
| EF (mean ± SD) | 52.2 ± 13.4 | 61.8 ± 9.4 | 0.005 |
| Length of vegetation | 10.4 ± 7.4 | 16.5 ± 10.9 | 0.2 |
| Width of vegetation | 6.6 ± 5.6 | 8.4 ± 6.3 | 0.5 |
| Aortic root abscess | 2 (15.4) | 5 (6.7) | 0.2 |
| **Laboratory data** | | | |
| Creatinine on admission (mg/dL) | 1.8 ± 2.4 | 1.7 ± 2.1 | 0.8 |
| Creatinine on discharge (mg/dL) | 1.7 ± 1.4 | 1.8 ± 2.2 | 0.9 |
| Hemoglobin on admission (g/L) | 9.6 ± 1.0 | 8.8 ± 1.9 | 0.07 |
| Hemoglobin on discharge (g/L) | 10.2 ± 1.1 | 10.3 ± 1.3 | 0.9 |

PE, pericardial effusion; IE, infective endocarditis; SD, standard deviation; EF, ejection fraction.
[a] Species.

study, we found similar results, as younger patients had a significantly higher incidence of PE than older patients; however, we did not demonstrate a difference in renal impairment between patients with and without PE. We also demonstrated that compared with IE patients without PE, IE patients who develop PE have higher rates of sepsis and complications (reflected in a higher rate of referral to surgery) and a higher overall in-hospital mortality.

The presence of a substantial PE did not appear to change the course of the illness, as patients with substantial PE (≥moderate PE as shown by echocardiography) had similar rates of complications and overall mortality as patients with mild PE.

The most recent study conducted by Regueiro et al[10] showed that the incidence of PE in native valve IE was lower than previously found, and they also found that PE in the setting of native valve IE was associated with a higher in-hospital heart failure but not a higher mortality. These results are quite different from ours, because although patients with PE, in our study, had a higher incidence of heart failure than patients without PE, yet the difference was not statistically significant, maybe because in Regueiro study, they used larger sample volume, and they only included patients with native valve IE. On the other hand, they found that patients with PE and IE showed a higher need for surgical correction of patients' valvular mechanical lesions, and our study showed similar results. Regueiro et al showed that most PE and IE patients had mild or moderate PE (99.5%), and only six patients (0.5%) had severe PE. In this study, we also found that only four patients (1.1%) had large (severe) PE while the rest of patients had either mild or moderate PE. Our results agree with Regueiro results in regard to the lack of difference in the clinical outcome between patients with and without substantial PE.

The most commonly encountered prostheses in patients with IE and PE in our series were mitral valve (MV) prostheses. This is because most MVR surgery is performed for advanced rheumatic MV disease; the MV is the valve most commonly affected by rheumatic fever.

Compared with patients with native valve endocarditis and PE, patients with prosthetic endocarditis and PE had lower rates of heart failure, sepsis, and kidney injury. This might have been due to earlier diagnosis and more aggressive intervention in prosthetic endocarditis patients. On the other hand, compared with patients without prostheses, patients with prostheses had higher rates of mycotic aneurysms and intracranial hemorrahge.

The most important predictors of overall mortality were sepsis and intracranial hemorrhage. The presence of PE, per se, was not a predictor of mortality, yet the higher incidence of mortality observed in IE patients with PE as compared with IE without PE is probably attributable to the higher sepsis rate in IE and PE patients.

**Table 3**
Outcome of patients with pericardial effusion with and without cardiac prosthetic material.

| Variable | PE and prosthesis IE ($n = 13$), No. (%) | PE and native valve IE ($n = 75$), No. (%) | $p$ value |
|---|---|---|---|
| **Complications** | | | |
| CHF NYHA class III-IV | 3 (23.1) | 21 (28.0) | 0.6 |
| Need for dialysis | 0 (0) | 3 (4.0) | 0.7 |
| Sepsis | 0 (0) | 7 (9.3) | 0.4 |
| Splenic infarcts | 2 (15.4) | 12 (16.0) | 0.6 |
| Splenic abscess | 1 (7.7) | 7 (9.3) | 0.7 |
| Pulmonary infarcts | 1 (7.7) | 8 (10.7) | 0.6 |
| Mycotic aneurysm | 2 (15.4) | 3 (4.0) | 0.1 |
| Intracranial hemorrhage | 2 (15.4) | 4 (5.3) | 0.2 |
| Peripheral embolization | 5 (38.5) | 29 (38.7) | 0.8 |
| **Mortality** | 5 (38.5) | 26 (34.7) | 0.8 |
| **Response to antibiotic therapy** | 4 (30.8) | 34 (45.3) | 0.2 |
| **Indication for surgery** | 10 (76.9) | 64 (85.3) | 0.3 |

CHF, congestive heart failure; NYHA, New York Heart Association; PE, pericardial effusion; IE; infective endocarditis.

### 4.1. Limitations

IE patients who underwent cardiac surgical procedures in the course of their illness should have undergone pericardial tissue sampling for pathological identification of the etiology of pericardial involvement. Unfortunately, this was not done, as some patients were recruited retrospectively from the registry files. This retrospective recruitment of patient data is considered another limitation of the study.

## 5. Conclusion

Despite that PE in IE patients did not predict mortality, yet this study showed that the presence of PE during active IE indicates a poorer prognosis with higher complication rates. This finding suggests the need for earlier active and aggressive intervention for such patients. The presence of a prosthetic valve in IE patients with PE did not increase the risk of complications and did not worsen the outcomes.

## Conflicts of interest

All authors have none to declare.

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