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Clinical Investigation

Can Asthma Cause Pericardial Effusion? Insights Into an Intriguing Association

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Abstract

Background: Pericardial effusion (PE) is a commonly encountered condition in clinical practice, but its etiology can be difficult to identify, with many cases remaining classified as idiopathic. This study aimed to investigate whether an association exists between asthma and idiopathic PE (IPE).

Methods: Patients who had been diagnosed with PE in the authors' outpatient cardiology clinics between March 2015 and November 2018 were retrospectively analyzed. The study population was divided into 2 groups—non-IPE (NIPE) and IPE—based on whether a cause had been identified. Demographic, laboratory, and clinical data for the 2 groups were examined statistically.

Results: A total of 714 patients were enrolled in the study after exclusion of 40 cases. Of these 714 patients, 558 were allocated to the NIPE group and 156 to the IPE group (NIPE group median [IQR] age, 50 [41-58] years vs IPE group median [IQR] age, 47 [39-56] years; $P = .03$). Asthma was significantly more prevalent among patients in the IPE group than among those in the NIPE group (n = 54 [34.6%] vs n = 82 [14.7%]; $P < .001$). In multivariate logistic regression analysis, asthma (odds ratio, 2.67 [95% CI, 1.53-4.67]; $P = .001$) was found to be an independent predictor of IPE. In the IPE group, patients with asthma had either mild or moderate PE, with the right atrium being the most common location in these patients.

Conclusion: Asthma was an independent predictor of mild to moderate IPE. The right atrium was the most frequently encountered location for PE in patients with asthma.

Keywords: Pericardial effusion; asthma; echocardiography; physiopathology

Introduction

The pericardium responds to various etiologies in a relatively nonspecific manner by filling with fluid. Therefore, any disease that involves the pericardium may result in pericardial effusion (PE). Infections, malignancy, systemic autoimmune diseases, congestive heart failure, kidney failure, cirrhosis, hypothyroidism, myocardial infarction, radiation therapy, and drugs are the established causes of PE.[1-4]

Reports on the etiologic distribution of PE vary from study to study, and a considerable number of cases in these studies are classified as "idiopathic pericarditis" in the absence of identifiable causes.[1,5-10] Certainly, the term *idiopathic* implies a lack of scientific surety regarding cause, but it could also imply underdiagnosis of certain underlying causes. The authors postulate that the number of idiopathic cases could be reduced if previously undefined causes were reclassified based on the correct etiologic diagnosis. For example, viruses are generally presumed to be the underlying cause of idiopathic PE (IPE), but some case reports in the literature have demonstrated the development of PE in the setting of asthma.[3,11-14] Like pericardial disease, asthma is a common clinical condition, and its underlying pathophysiology is not fully understood because of the condition's complexity. This study aimed to investigate whether an association exists between asthma and IPE.

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Patients and Methods

In this study, the authors retrospectively reviewed the charts of 751 patients aged 18 to 65 years from their outpatient cardiology clinics in whom PE had been diagnosed between March 2015 and November 2018. Of these 751 patients, those whose PE had an established etiology were assigned to the non-IPE (NIPE) group, whereas those whose disease did not have an identifiable cause were assigned to the IPE group. To detect manifestations of a possible underlying disease, the patients in the IPE group were followed for at least 1 year after PE diagnosis.

Etiologies leading to NIPE include infectious agents (eg, viral, bacterial, fungal, or protozoal), autoimmune diseases (eg, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjögren syndrome, Churg-Strauss disease, familial Mediterranean fever, inflammatory bowel disease), malignancy, radiation therapy, kidney failure, congestive heart failure, nephrotic syndrome, myocardial infarction, cirrhosis, hypothyroidism, hyperthyroidism, trauma (direct or indirect pericardial injury, including penetrating or blunt chest wall injury and aortic dissection), and drug hypersensitivity (eg, procainamide, hydralazine, isoniazid, minoxidil, penicillin, methyldopa).[3,11] The patients in the IPE group had none of these conditions or factors, nor did they meet the following criteria: white blood cell count higher than 10×10^9/L; erythrocyte sedimentation rate higher than 20 mm/h; C-reactive protein level higher than 50 mg/L; positive rheumatoid factor; positive antinuclear antibodies; or the presence of obstructive sleep apnea syndrome, pulmonary hypertension, or pregnancy.[15-18] Hypertension, diabetes, hyperlipidemia, and smoking were not considered exclusion criteria in this study. The study was approved by the Diskapi Yıldırım Beyazit Education and Research Hospital Clinical Research Review Board (approval No. 68/16, July 22, 2019).

Clinical records for all patients underwent comprehensive clinical investigation to detect any possible explanation for PE. The demographic and echocardiographic variables together with laboratory values were reviewed, as well. Patients with asthma who had been diagnosed by a pulmonologist searching for a possible pulmonary cause of previously diagnosed PE were noted. Asthma was diagnosed by a pulmonologist according to clinical findings, pulmonary function tests, and the criteria described in the Global Initiative for Asthma guidelines.[19] Pulmonary function testing was performed according to European Respiratory Society consensus standards.[20]

Abbreviations and Acronyms

IL	interleukin
IPE	idiopathic pericardial effusion
NIPE	nonidiopathic pericardial effusion
NLRP3	nucleotide-binding oligomerization domain–like receptor family, pyrin domain–containing 3
PE	pericardial effusion
TRAPS	tumor necrosis factor receptor–associated periodic syndrome

Echocardiographic evaluation of each patient was performed using standard 2-dimensional and Doppler evaluation according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[21] The Philips HD11XE ultrasound machine was used. Pericardial effusion was assessed quantitatively by measuring the end-diastolic echo-free space between the visceral and parietal pericardial layers from the parasternal long-axis, parasternal short-axis, and apical views. According to this measurement, PE was classified as mild (<10 mm), moderate (10-20 mm), or large (>20 mm).[4] Pulmonary artery systolic pressure was evaluated based on tricuspid systolic blood flow by continuous-wave Doppler ultrasound. It was calculated by adding the estimated right atrial pressure to the transtricuspid gradient, which was derived from the tricuspid regurgitation velocity, using the Bernoulli equation (transtricuspid pressure gradient = [tricuspid regurgitation velocity]$^2 \times 4$).[22]

Statistical Analysis

Categorical variables were described as frequency and percentage. Normally distributed continuous variables were expressed as mean (SD), and nonnormally distributed continuous variables were presented as median (IQR). The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. The χ^2 test, independent-samples *t* test, and Mann-Whitney *U* test were used for intergroup comparisons. Because of the retrospective, nonrandomized nature of the study, a propensity score analysis was conducted to overcome any possible selection biases and potential confounding in the comparison of patients with IPE and NIPE. A propensity score was calculated for each patient by using a multivariate logistic regression model that included the type of PE as the dependent variable and the following variables as the covariates: age, sex, body mass index, hemoglobin, serum glucose, albumin, creatinine, glomerular filtration rate, smoking status, asthma, hypertension, diabetes, and

hyperlipidemia. After propensity score estimation, propensity score matching was applied in a 1:1 ratio with a match tolerance value of 0.5. Possible predictors with $P<.20$ in the univariate analysis were further entered into multivariate logistic regression analysis (backward stepwise method) to determine independent predictors of IPE. The model fit was assessed by using the Hosmer-Lemeshow goodness-of-fit test. Results were presented as odds ratios and 95% CIs. $P<.05$ was considered statistically significant. IBM SPSS, version 24.0, software was used for the statistical analysis.

Results

Of 751 patients in this study, 558 patients were found to have an established etiology for PE and were enrolled in the NIPE group (261 [46.8%] women; median [IQR] age, 50 [41-58] years). Of the remaining 193 patients who did not have an identifiable cause for PE, 31 patients were excluded for other reasons, including C-reactive protein level higher than 50 mg/L, positive antinuclear antibodies, positive rheumatoid factor, obstructive sleep apnea, and pulmonary hypertension. Another 6 patients who developed malignancy or an autoimmune disease during clinical follow-up were also excluded. Therefore, 156 patients were enrolled in the IPE group (79 [50.6%] women; median [IQR] age, 47 [39-56] years). Of these patients, 78 had mild PE, 74 had moderate PE, and 4 had large PE.

The baseline demographic, clinical, and laboratory characteristics of both groups are summarized in Table I. There were no significant differences between the 2 groups with respect to sex; body mass index; smoking status; the presence of hyperlipidemia or diabetes; or glomerular filtration rate, creatinine, and glucose levels ($P>.05$). In the NIPE group, age was significantly higher ($P=.03$) and hypertension was significantly more common ($P=.05$). Hemoglobin and albumin levels were found to be significantly lower in the NIPE group than in the IPE group ($P=.01$ and $P=.02$, respectively). Asthma was significantly more common among patients in the IPE group than among those in the NIPE group ($P<.001$). In multivariate logistic regression analysis, asthma (odds ratio, 2.98 [95% CI, 1.98-4.48]; $P<.001$) was found to be an independent predictor of IPE (Table II).

In the IPE group, patients with asthma had mostly mild PE (77.8%), followed by moderate PE (22.2%); there were no instances of large PE. Effusions were mostly loculated in front of the right atrium; no instances of diffuse effusion were seen (Table III).

The distribution of the established etiologies leading to NIPE is presented in Table IV. Infection was found to be the leading cause, followed by malignancy, congestive heart failure, kidney failure, autoimmune diseases, hypothyroidism, cirrhosis, post–myocardial infarction, trauma, hyperthyroidism, and history of radiation therapy, respectively.

After propensity score matching, the NIPE group consisted of 156 patients. Age and albumin levels were balanced between the IPE and NIPE groups ($P>.05$). Table V shows the comparisons of patient characteristics in the propensity-matched cohort. The multivariate logistic regression analysis identified asthma as an independent risk factor associated with the development of IPE (odds ratio, 2.67 [95% CI: 1.53-4.67]; $P=.001$) (Table VI).

Discussion

The present study demonstrates that asthma was considerably more prevalent in patients with IPE than in patients with NIPE. In addition, asthma was shown to be an independent predictor of IPE, indicating that the risk of mild to moderate PE may be higher in patients with asthma. Excluding some rare case reports, it has not been proposed that asthma is involved in the etiology of PE. Therefore, to the authors' knowledge, this study is the first to reveal a causal relationship between asthma and IPE.

In the literature, some of the case reports attributed the presence of pericarditis in patients with asthma to cromoglycate use, but they mainly focused on a scenario whereby asthma and eosinophilia leading to eosinophilic pericarditis becomes the mainstay. The diagnosis was made after exclusion of infectious, malignant, and vasculitic causes. As the underlying pathophysiology, a largely unknown immunologic mechanism was proposed.[12-14]

Pericardial effusion occurs either as an isolated disease or as a component of a systemic illness.[3,4,11] Although reports on the frequency of etiologic distribution varies from study to study, a considerable number of PE cases (up to 48%) are referred to as idiopathic in each study in the absence of fully elucidated identifiable causes.[1,5-10] From this perspective, correlated with the diagnostic approach, these reports show a widely dispersed frequency

TABLE I. Baseline Demographic, Clinical, and Laboratory Characteristics of the Analyzed Study Population

Characteristic	IPE (n = 156)	NIPE (n = 558)	Total (N = 714)	*P* value
Age, median (IQR), y	47 (39-56)	50 (41-58)	49 (41-58)	.03[a]
Female sex, No. (%)	79 (50.6)	261 (46.8)	340 (47.6)	.39
Body mass index, median (IQR)	25.37 (23.83-26.81)	25.47 (24.30-26.93)	25.46 (24.17-26.90)	.12
Smoking status, No. (%)	35 (22.4)	150 (26.9)	185 (25.9)	.26
Asthma, No, (%)	54 (34.6)	82 (14.7)	142 (19.9)	<.001[a]
Hypertension, No. (%)	35 (22.4)	171 (30.6)	206 (28.9)	.045[a]
Diabetes, No. (%)	30 (19.2)	146 (26.2)	176 (24.6)	.08
Hyperlipidemia, No. (%)	29 (18.6)	91 (16.3)	120 (16.8)	.50
Hemoglobin, median (IQR), g/L	137 (129-145)	135 (119-145)	135 (123-145)	.01[a]
Glomerular filtration rate, median (IQR), mL/min/1.73 m^2	97.1 (93.3-102.7)	95.8 (91.5-103.8)	96.4 (92-103.5)	.056
Creatinine, median (IQR), μmol/L	83.10 (76.02-94.59)	83.10 (73.38-96.36)	83.10 (74.26-95.47)	.76
Albumin, median (IQR), g/L	400 (380-420)	395 (368-420)	400 (370-420)	.02[a]
Glucose, median (IQR), mmol/L	4.66 (4.22-5.22)	4.77 (4.33-5.33)	4.77 (4.27-5.27)	.12

IPE, idiopathic pericardial effusion; NIPE, nonidiopathic pericardial effusion.

[a] $P < .05$ was considered statistically significant.

TABLE II. Backward Stepwise Logistic Regression Analysis to Assess Predictors of Idiopathic Pericardial Effusion

Parameter	OR (95% CI)	*P* value
Age	0.99 (0.96-1.02)	.45
Body mass index	1.04 (0.95-1.14)	.38
Asthma	2.79 (1.82-4.26)	<.001[a]
Hypertension	0.87 (0.54-1.41)	.57
Diabetes	0.87 (0.46-1.63)	.67
Hemoglobin	0.92 (0.78-1.08)	.32
Glomerular filtration rate	0.99 (0.95-1.03)	.48
Creatinine	0.89 (0.24-3.34)	.87
Albumin	0.97 (0.91-1.03)	.25
Glucose	1.00 (0.99-1.02)	.78
Last step[b]		
Asthma	2.98 (1.98-4.48)	<.001[a]

OR, odds ratio.

[a] $P < .05$ was considered statistically significant.
[b] *Last step* defines the result of multivariate logistic regression analysis using a backward stepwise method, as all variables in the table were entered in the first step of regression analysis and only asthma was retained in the last step.

TABLE III. Distribution of Patients With Asthma in the IPE Group According to the Grade and Localization of PE

Patients with asthma in the IPE group (n = 54)	No.	%
PE grade		
Mild	42	77.8
Moderate	12	22.2
Large	0	0
Localization of PE		
Right atrium	32	59.3
Right heart chamber	19	35.2
Right heart chamber and left ventricle	3	5.5
Diffuse	0	0

IPE, idiopathic pericardial effusion; PE, pericardial effusion.

TABLE IV. Distribution of Patients in the NIPE Group by Etiology Leading to PE

NIPE group (n = 558)	No.	%
Active infection	101	18.1
Cancer	89	15.9
Congestive heart failure	85	15.2
Kidney failure	77	13.8
Autoimmune disease	56	10
Hypothyroidism	47	8.4
Chronic liver disease	30	5.4
Myocardial infarction	25	4.5
Trauma	21	3.8
Hyperthyroidism	15	2.7
History of radiation therapy	12	2.2

NIPE, nonidiopathic pericardial effusion; PE, pericardial effusion.

of idiopathic cases; a multidisciplinary diagnostic approach that includes more comprehensive and detailed clinical examination may reveal a higher number of idiopathic cases.

For years, viruses were considered to be the main vector involved in the unclarified etiology of IPE, but more recently, the nucleotide-binding oligomerization domain–like receptor family, pyrin domain–containing 3 (NLRP3) inflammasome-mediated impaired innate immune system is thought to be the mechanism responsible for some of these idiopathic cases.[3,11,23-26] The innate immune system responds immediately to various pathogen-associated and damage-associated molecular patterns via downstream activation of inflammasome, an intracellular platform. Inflammasome consists of an NLR; a caspase activation recruitment domain; and a final effector protein, caspase 1. The NLR contains different structures, with NLRP3 being the most ex-

TABLE V. Baseline Demographic, Clinical, and Laboratory Characteristics of the Analyzed Study Population After Propensity Score Matching

	IPE (n = 156)	NIPE (n = 156)	Total (N = 312)	*P* value
Age, median (IQR), y	47 (39-56)	48 (38-58)	47 (39-57)	.64
Female sex, No. (%)	79 (50.6)	79 (50.6)	158 (49.4)	.99
Body mass index, mean (SD)	25.32 (2.14)	25.73 (2.38)	25.53 (2.27)	.10
Smoking status, No. (%)	35 (22.4)	49 (31.4)	84 (26.9)	.07
Asthma, No. (%)	54 (34.6)	24 (15.4)	78 (25)	<.001[a]
Hypertension, No. (%)	35 (22.4)	55 (35.3)	90 (28.8)	.01[a]
Diabetes, No. (%)	30 (19.2)	49 (31.4)	79 (25.3)	.01[a]
Hyperlipidemia, No. (%)	29 (18.6)	30 (19.2)	59 (19.0)	.89
Hemoglobin, median (IQR), g/L	137 (129-145)	131 (119-142)	133 (125-142)	.001[a]
Glomerular filtration rate, median (IQR), mL/min/1.73 m^2	97.1 (93.3-102.7)	95.5 (88.4-104.5)	96.5 (92.1-103.73)	.07
Creatinine, median (IQR), μmol/L	83.07 (76.02-94.59)	81.33 (69.84-93.70)	83.10 (74.26-84.59)	.13
Albumin, median (IQR), g/L	400 (380-420)	400 (360-420)	400 (370-420)	.23
Glucose, median (IQR), mmol/L	4.66 (4.22-5.22)	4.77 (4.33-5.54)	4.72 (4.27-5.33)	.09

IPE, idiopathic pericardial effusion; NIPE, nonidiopathic pericardial effusion.

[a] $P < .05$ was considered statistically significant.

TABLE VI. Backward Stepwise Logistic Regression Analysis of Predictors of Idiopathic Pericardial Effusion After Propensity Score Matching

Parameter	OR (95% CI)	*P* value
Body mass index	0.98 (0.88-1.09)	.69
Smoking status	0.63 (0.37-1.08)	.09
Asthma	2.56 (1.44-4.54)	.001
Hypertension	0.77 (0.44-1.35)	.37
Diabetes	0.64 (0.27-1.48)	.30
Creatinine	0.70 (0.32-1.52)	.37
Albumin	1.03 (0.96-1.11)	.38
Glucose	1.00 (0.98-1.02)	.92
Last step[a]		
Asthma	2.67 (1.53-4.67)	.001[b]

OR, odds ratio.

[a] *Last step* defines the ending step of multivariate logistic regression analysis using a backward stepwise method as all variables in the table were entered in the first step of regression analysis and only asthma was retained in the last step.
[b] $P < .05$ was considered statistically significant.

tensively characterized. When NLRP3 is activated by pathogen-associated or damage-associated molecular patterns, the cleavage of pro–interleukin (IL)-1β to its biological active form, IL-1β, by caspase 1 occurs. Circulating IL-1β then stimulates a powerful inflammatory response by upregulating the prostaglandin production and recruiting neutrophils to the site of injury.[23-28]

If changes develop in the innate immune system mediated through inflammasomes, unprovoked, periodic, multisystemic inflammation manifests as autoinflammatory disease—that is, a heterogeneous group of diseases that includes familial Mediterranean fever and tumor necrosis factor receptor–associated periodic syndrome (TRAPS), with recurrent pericardial disease a common feature in both conditions. Intriguingly, tumor necrosis factor receptor superfamily member 1A (*TNFRSF1A*), the gene encoding TRAPS, has also been detected in patients with isolated idiopathic recurrent pericarditis.[23-26,29] Beyond these similarities, anakinra, an IL-1 receptor antagonist, has been shown in many studies to be effective in controlling idiopathic recurrent pericardial disease. Currently, whether an impaired innate immune system exerting the proinflammatory effect of IL-1β and recruitment of neutrophils might be the main underlying mechanism in at least a subset of patients with idiopathic pericardial disease is debatable.[24-26,28-33]

Asthma is a chronic inflammatory airway disease characterized by heterogeneity. Like pericardial disease, the underlying pathophysiology is not fully understood because of the condition's complexity. Recently, apart from the classic eosinophilic phenotype, a new subtype of asthma was identified: neutrophilic asthma. This subtype accounts for 15% to 25% of asthma cases, and since its discovery, researchers have focused on understanding its main underlying mechanism.[34-38] Unlike with the eosinophilic phenotype, augmented expression of NLRP3-inflammasome and caspase, with increased release of IL-1β in patients with neutrophilic asthma, has been found. In these patients, the activation of the NLRP3-inflammasome cascade with subsequent cleavage of pro–IL-1β to its active form has emerged as the underlying pathophysiologic mechanism.[39-44]

Given the recent focus on the importance of the innate immune system in pericardial diseases, it is noteworthy that both idiopathic pericardial disease and neutrophilic asthma are assumed to proceed along an NLRP3-inflammasome–driven pathway. On this basis, the authors hypothesize that the concurrence of asthma and PE may not implicate a comorbid condition. Rather, it may imply that PE is a sign of asthma. Accordingly, the authors suggest that the proposed NLRP3-inflammasome–driven pathway, particularly in neutrophilic asthma, may pave the way for development of pericardial signs. Therefore, apart from a few previous case reports proposing eosinophilic asthma, the authors underline neutrophilic asthma in the etiopathogenesis of IPE.

With respect to pathophysiology, asthma is characterized by repeated attacks that in turn may lead to hypoxia. The hypoxic nature of this disease may initiate a cascade of complex reactions that result in endothelial dysfunction, fibrosis, and constriction of pulmonary arterioles (with eventual pulmonary hypertension). Therefore, asthma may be associated with intermittent or even sustained pulmonary hypertension in patients for whom hypoxia persists over a long period.[45,46] These detrimental consequences of asthma may be another possible explanation for the development of PE in patients with asthma, with some previous experimental studies having reported a hemodynamic link between pulmonary hypertension and PE based on the leading hypothesis that the compromised drainage of pericardial fluid and increased transudation of myocardial interstitial fluid result from higher mean right atrial pressure in the presence of pulmonary hypertension.[47,48]

In the authors' view, cases of PE classified as idiopathic are not really idiopathic; rather, their cause has not yet been clarified. More comprehensive clinical evaluation establishing a specific cause for the PE may reduce the number of cases classified as idiopathic. The results of this study confirming this possible relationship between asthma and pericardial effusion hold promise in contributing to the etiology of PE for future studies. This relationship can provide a new, easily applicable echocardiographic parameter for follow-up of patients with asthma.

In the present study, PE was mostly mild and loculated in front of the right atrium in patients with asthma. Consistent with that finding, a previous report had stated that the right atrium is a preferred location for mild PE because the collection of pericardial fluid there is easy because intracardiac pressure is lowest in the right atrium during the cardiac cycle.[49] Although mild PE is not hemodynamically important clinically, it should not be neglected because it may reflect a noncardiac condition such as asthma.

This study has both strengths and limitations. First, it included only those patients who did not have any disease or clinical condition that could be suspected in the etiology of PE. The patients were also monitored throughout the year following initial diagnosis of PE to establish any possible developing disease that could be suspected in the etiology of PE. Therefore, the internal validity of the study was strengthened by limiting the number of confounding factors. In addition, the direction of the effect in the regression analysis was justified based on a hypothesis that relies on a reasonable pathophysiologic basis to enhance the probability of a cause-and-effect relationship.

With regard to the limitations, this study had a retrospective design and was based on a single-center registry. In addition, in the IPE group, pericardiocentesis was not performed in patients with asthma because they were hemodynamically stable and exhibited mild to moderate PE that did not change significantly during clinical follow-up. Finally, the prognostic value of asthma in PE was not explored in the absence of longer-term follow-up results.

Conclusion

In this study, asthma was found to be a frequently encountered phenomenon in patients with IPE, pointing to a significant, independent relationship between asthma and mild to moderate PE. This finding supports the hypothesis that some asthma phenotypes may be an unclarified cause of mild to moderate PE. Future studies are needed to explore this possible association and to unveil a cause in the etiology of IPE. Further investigations may also provide diagnostic and prognostic direction for the determination of asthma phenotypes based on echocardiography-guided evaluation of PE.

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