Dicle Tıp Dergisi /
Dicle Medical Journal

2014; 41 (4): 629-634
doi: 10.5798/diclemedj.0921.2014.04.0489

ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Etiology, diagnosis and management of severe pericardial effusion: A single center experience

Ciddi perikardiyal efüzyonun etiyolojisi, tanısı ve yönetimi: Tek merkez deneyimi

Mehmet Aytürk[1], Ahmet Göktuğ Ertem[2], Mustafa Duran[2], Selçuk Özkan[1], Hamza Sunman[3], Harun Kılıç[4], Ekrem Yeter[3]

ABSTRACT

Objective: To show etiology, diagnostic methods, and treatment options of patients with severe pericardial effusion determined after echocardiography.

Methods: In this study, we retrospectively analyzed etiology, diagnosis and treatment options of 43 patients with severe pericardial effusions (i.e. effusions more than 20 mm either in front of the right ventricle or posterior to left ventricle as assessed by transthoracic echocardiography). The pericardiocentesis procedures were performed via subxiphoid approach. Glucose, protein, lactate dehydrogenase levels, polymerase chain reaction for tuberculosis, cytological, microbiological examinations and cultures were obtained from pericardial fluid.

Results: Cardiac tamponade was diagnosed in 23 patients (54%) and pericardiocentesis was immediately performed in these cases. Twenty patients who were unresponsive to empirical treatment, underwent pericardiocentesis to evaluate etiology and treatment.. Pericardial fluid was found to be exudate in 36 patients (83.7%) and transudate in 7 patients (16.2%). The most common causes were malignancy (26%), and uremia (16%) while idiopathic cases constituted 23% of the patient group. While malignant pericardial effusion was more common in males, idiopathic etiology and uremia were more common in female patients.

Conclusion: Pericardiocentesis is the gold standard for clarifying the etiology and is also a lifesaving measure for cardiac tamponade. Delineating the specific etiology is particularly important for cases that do not respond to empirical treatment. A thorough history and physical examination, together with pericardiocentesis in selected cases will enable the accurate diagnosis of specific etiology and starting the treatment for this etiology.

Key words: Pericardiocentesis, echocardiography, effusion

ÖZET

Amaç: Ekokardiyografi sonrasında saptanan ciddi perikardiyal efüzyonu olan hastalarda etiyoloji, tanı metotları ve tedavi seçeneklerini göstermektir.

Yöntemler: Bu çalışmada geriye dönük olarak, ciddi perikardiyal efüzyonu olan 43 hastayı (transtorasik ekokardiyografide sağ ventrikül önünde veya sol ventrikül arkasında 20 mm'den fazla olan efüzyon, kalbi çevreleyen efüzyon) etiyoloji, tanı ve tedavi seçenekleri açısından analiz ettik. Perikardiyosentez prosedürü subksifoid yol üzerinden yapıldı. Perikardiyal sıvıdan glukoz, protein, laktat dehidrojenaz, tüberküloz için polimeraz zincir reaksiyonu, sitolojik, mikrobiyolojik testler ve kültür çalışıldı.

Bulgular: Yirmi üç hastada (%54) hastada kardiyak tamponat tanısı konuldu ve erken perikardiyosentez uygulandı. Ampirik tedaviye yanıtı olmayan yirmi hastaya, etiyoloji ve tedaviyi yönetmek açısından perikardiyosentez uygulandı. Otuzaltı hastada (%83,7) perikardiyal sıvı eksüda iken, 7 hastada (%16,2) transüda idi. En sık görülen nedenler malignensi (%26), ve üremi (%16) iken etiyolojisi belirlenemeyen hastalar da %23'ü oluşturuyordu. Malign perikardiyal efüzyon erkeklerde sık görülürken, üremiye bağlı olan ve nedeni belirlenemeyen effüzyonlar kadın hastalarda sık görülmekteydi.

Sonuç: Perikardiyosentez, kardiyak tamponatta hayat kurtarıcı bir tedavidir ve etiyolojiyi netleştirmede altın standarttır. Özellikle, ampirik tedavinin başarısız olduğu durumlarda, spesifik etiyolojiyi saptamak önemlidir. Dikkatli alınan medikal öykü, detaylı fizik muayene ve gerekirse perikardiyosentez prosedürü, spesifik etiyoloji için tanı koymada ve hastalığın yönetiminde yardımcı olacaktır.

Anahtar kelimeler: Perikardiyosentez, ekokardiyografi, efüzyon

[1] Keçiören Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Ankara, Türkiye
[2] Ankara Atatürk Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Ankara, Türkiye
[3] Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Kardiyoloji kliniği, Ankara, T Türkiye
[4] Sakarya Üniversitesi, Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Sakarya, Türkiye

Yazışma Adresi /Correspondence: *Ahmet Göktuğ Ertem,*
Keçiören Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Ankara, Türkiye Email: agertem@hotmail.com

Geliş Tarihi / Received: 24.07.2014, Kabul Tarihi / Accepted: 04.11.2014

INTRODUCTION

Early and definitive diagnosis is crucial in patients with pericardial effusion. The major pathology that causes pericardial effusion is the imbalance between production of pericardial fluid and its drainage. Subxiphoid percutaneous catheterization or surgical drainage are traditional approaches in patients with severe pericardial effusion. Pericardiocentesis is gold standard method for assessment of specific etiology. Thoracotomy can also be performed as a last resort when pericardiocentesis is difficult due to small amount of effusion [1,2].

Pericardiocentesis is often the method of choice in patients with cardiac tamponade or in symptomatic patients who do not respond to standard therapy. In addition, it is the most convenient approach when there is a high degree of suspicion for purulent fluid or malignancy.

In this study, we aimed to retrospectively evaluate clinical and laboratory findings of patients with established severe pericardial effusion and specific etiologies in cases, to whom pericardiocentesis was performed.

METHODS

In this study, we retrospectively analyzed the etiology, diagnostic approach and management of 43 patients admitted with severe pericardial effusion (i.e. effusions more than 20 mm either in front of the right ventricle or posterior to left ventricle as assessed by transthoracic echocardiography) and underwent pericardiocentesis in our center between January 2010 and January 2014.

Twenty-eight patients underwent pericardiocentesis due to cardiac tamponade and 15 patients who did not respond empiric therapies underwent pericardiocentesis for diagnostic evaluation. Cardiac tamponade was defined as hemodynamically significant cardiac compression (elevated central venous pressure, pulsus parodoxus, tachycardia, hypotension), which is caused by pericardial fluid compressing right ventricle during diastole [6].

All pericardiocentesis procedures were performed using subxiphoid approach. The puncture site (1 mm left to the costo-xiphoid angle) was anesthetized by lidocaine (1-2%). A 18 G punction needle was inserted at the right side of xiphoid and advanced subcostally, directed towards left shoulder with continuous suction applied to a 10 cc syringe, which was attached to the hub of the needle. The needle was advanced slowly towards the left shoulder, while applying negative pressure on the syringe until the fluid was visualized. When fluid was seen, we inserted the floppy guide-wire and advanced the 6F dilatator and widened the skin. After withdrawing the dilatator, we inserted a pigtail catheter with multiple side holes over this wire. We confirmed the position of the catheter with the echocardiographic guidance during the procedure.

All samples were submitted for cytological examination, microbiological culture, and biochemical tests for glucose and protein levels, lactate dehydrogenase (LDH), and polymerase chain reaction (PCR) analyses. Light‘s criteria were used to distinguish exudates (fluid protein level 3.0 g/dl, fluid protein/serum protein ratio 0.5, fluid LDH 200 mg/dl; fluid/serum LDH ratio 0.6, fluid cholesterol measurement >45 mg/dl) from transudates [7].

Patients with pericardial efussion and recent history of respiratory tract infection were considered to have viral pericarditis after excluding other possible etiologies. The diagnosis of idiopathic pericarditis was made for patients who did not have a history of respiratory tract infection, respond medical treatment and whose pericardial effusion did not recur. In patients with idiopathic pericarditis, no further diagnostic tests were performed as stated in the guidelines of European Society of Cardiology (ESC) [8].

Statistical analysis

All statistical analyses were performed using SPSS for Windows (release 15.0, SPSS Inc., Chicago, Illinois). Descriptive analysis was performed. Median, minimum, maximum and percentages were given for each parameter.

RESULTS

Demographic characteristics of the patients were shown in Table 1. The study enrolled 43 patients (22 men and 21 women) and the median age was 65 (44-84) years. Thirty-six patients (84%) were diagnosed to have exudative pericardial effusion,

and seven patients (16%) had idiopathic pericarditis with transudate effusion. In 7 patients, underlying etiology was renal failure, and in 11 patients it was malignancy-associated effusion. Eight of these patients were diagnosed to have lung adenocarcinoma, 1 patient had lung squamous cell carcinoma, and 1patient had lung small cell carcinoma. Moreover, 1 patient was diagnosed with lymphoma according to cytological examination. In another patient, we showed thickening of colonic wall on abdominal ultrasonographic examination, but the patient refused to have further investigation. In 3 patients, pericardial effusion was associated with connective tissue disorders (two patients were diagnosed as rheumatoid arthritis and 1 patient had systemic lupus eritematozus (SLE)).

Table 1. Demographical and laboratory characteristics of study subjects

	Median	Minimum-Maximum
Age (years)	65	44-85
Urea (mg/dl)	73	15-224
Creatinine (mg/dl)	1.1	0.6-6.4
White blood cell (mm^{-3})	9.5	3.9-23.6
Haemoglobin (g/dl)	11	7.9-14.3
Serum protein (g/dl)	6	4-10.2
Serum LDH (U/l)	251	173-375
Fluid LDH (U/l)	377	75-4238
Fluid glucose (mg/dl)	99	32-192
Fluid protein (g/dl)	3.8	1.3-8.1
Sedimentation rate (mm/h)	32	4-222
C reactive protein (mg/l)	44	10-121
TSH (mIU/L)	0.92	0.01-10.3
Exudative (n, %)	36 (84%)	

LDH: Lactate dehydrogenase, TSH: Thyroid stimulating hormone

Still another patient with pericardial effusion had hypothyroidism. Three patients had bacterial pericardial effusion. One of them was diagnosed as tuberculous pericarditis. *Staphylococcus aureus* and *Enterococcus faecalis* were identified in pericardial fluid cultures obtained from other two patients. In 1 patient who had a history of temporary pacemaker implantation due to atrioventricular block, there was severe pericardial effusion, secondary to right ventricular perforation. Six patients were diagnosed with viral pericarditis.

DISCUSSION

It is well known that there are many causes of pericardial effusion, which may present as acute pericarditis. Among the etiologies of pericardial effusion, autoimmune, infectious, and inflammatory conditions are the main reasons [9]. Three prospective large scale studies provided valuable information about etiology of pericardial effusion [10-12]. However, there is a discrepancy between these studies, in terms of accurate definition of severe pericardial effusion. In our series we described severe pericardial effusion as effusion over 20 mm.

According to the study by Colombo et al, which included 20 patients, 44% of the participants presented with cardiac tamponade. Neoplastic (44%), idiopathic (32%) conditions and uremia (20%) were found to be main reasons that cause cardiac tamponade. In a study by Corey et al, which consisted of 57 patients, percentage of cardiac tamponade among patients was not mentioned. All samples were specifically evaluated for cytology and culture. The percentage of identifying etiology was higher when compared to other studies. Etiology was not clear in 4 patients only. The most common conditions leading to pericardial effusion were found to be malignancy (23%), viral infection (14%), inflammation induced by radiation therapy (14%), connective tissue disorder (12%) and uremia (12%). They demonstrated that further cytological evaluation on fluid samples obtained from patients with pericardial effusion could cause a shift from idiopathic reasons to viral reasons in terms of etiology.

In a study by Sagrista et al, which consisted of 322 patients, 132 patients had moderate, and 190 patients had severe pericardial effusion. Among them prevalence of cardiac tamponade was found to be 37%. In their study, idiopathic (16%), iatrogenic (16%) and neoplastic conditions (13%) were designated as common causes of pericardial effusion. In another study by Basar et al, which consisted of 104 patients with established moderate to severe pericardial effusion, idiopathic conditions were found

to be the main cause of pericardial effusions. They also showed that malignancy, congestive heart failure and tuberculosis were other major etiologies that might lead to pericardial effusion. In this study, 46 patients who did not respond to empiric therapies were referred to pericardiocentesis [13]. Both studies enrolled the patients with established moderate pericardial effusion. These studies demonstrated that there was a high prevalance of idiopathic pericardial effusion among patients presented with mild to moderate effusion.

In our series, prevalence of cardiac tamponade (23 patients, 54%) was higher than the other studies. The most common conditions which caused effusion were malignancy (26%), idiopathic (23%) and uremia (12%), respectively. Our results were consistent with Colombo's. According to our series, prevalance of malignant effusion was higher in male patients when compared to women. In contrast, uremia and idiopathic conditions were the most common causes in women (Table 2).

Table 2. Etiologies of pericardial effusion according to gender

	Male (n=22) n (%)	Female (n=21) n (%)	Total (n=43) n (%)
Malignancy	8 (59)	3 (14)	11 (26)
Renal failure	3 (13)	4 (19)	7 (16)
Idiopathic	4 (18)	6 (28)	10 (23)
Viral	3 (13)	4 (19)	7 (16)
Bacterial	1 (4)	1 (4)	2 (4)
Tuberculosis	1 (4)	0 (0)	1 (2)
Connective tissue disease	0 (0)	3 (14)	3 (7)
Hypothyroidism	1 (4)	0 (0)	1 (2)
Iatrogenic	1 (4)	0 (0)	1 (2)
Tamponade	15 (68)	13 (61)	28 (65)

In patients with malignancy, secondary pericardial effusion was mostly due to breast and lung cancers. Eleven patients presented with pericardial effusion secondary to malignancy. Four out of eleven patients were newly diagnosed with cancer according to cytology and CT scans. Cytology of three patients were consistent with adenocarcinoma and the remainder was diagnosed with lymphoma according to cytology results. One patient was referred to surgery due to recurrent severe pericardial effusions. His pericardial biopsy was consistent with metastatic lung adenocarcinoma. Three patients were diagnosed with lung adenocarcinoma and two patients had squamous cell carcinoma and small cell carcinoma respectively.

Cytology result is the single most important data for diagnostic process, however results of cytology can be controversial. Prior studies reported sensitivity rates of 67-92% [14-16]. In our series, despite the negative results of cytological examination, two patients were newly diagnosed with cancer after computerized tomography (CT) and biopsy. Prognosis and recurrence rates of pericardial effusion correlated with its origin.

Uremia is a common condition which causes pericardial effusion. There are two mechanisms by which uremia causes pericarditis; First, uremic pericarditis might be seen prior to dialysis or right after dialysis session which is mainly due to the inflammation of pericardial layers. Second, it might occur due to inadequate fluid withdrawal during hemodialysis which would end up with volume overload. In our series, 3 out of 7 patients presented with pericardial effusion due to uremia and referred to routine dialysis program. One patient, who was previously on dialysis program, had to increase the number of dialysis days because of recurrent pericardial effusion.

The prevalance of tuberculous (TBC) pericarditis is higher in developing countries, when compared to developed countries. TBC pericarditis in African countries is primarily seen in immuncompromised patients [17]. Although its prevalance has decreased dramatically in the last decades, TBC pericarditis can still be seen in rural areas of our country. The mortality rate of untreated acute pericarditis with effusion is substantially high and prevalance of constrictive pericarditis in those patients approaches 30-to-50% [17-19]. In our series, only 1 patient was diagnosed with TBC, after using PCR.

Purulent pericarditis in adults is a rare but fatal condition. In our series, 2 patients were diagnosed with bacterial pericarditis according to pericardial fluid and blood cultures. *Entereccus faecelis* was seen in one patient's culture and that patient was

treated with vancomycin and ciprofloxacin for more than 10 days. The other patient had methicillin sensitive *Staphylococcus aureus* proliferation in the culture and was treated with intravenous sulbactam/ampicillin. Both patients were discharged with full recovery.

Although viral pericarditis is the most common infection of the pericardium, definitive diagnosis of viral pericarditis is not possible without the examination of pericardial fluid by PCR or in-situ hybridization. In our series, 15 patients who had a history of respiratory tract infection, were diagnosed with viral pericarditis after excluding other etiologies. In addition seven patient were diagnosed with viral pericarditis due to inconclusive laboratory results. In those patients, we did not perform further analysis on pericardial fluids due to current recommendations of ESC.

Patients with established connective tissue disorder or hypothyroidism were also demonstrated in our series. According to the randomized controlled trials (RCTs) there was a positive correlation (3-80%) between hypothyroidism and pericardial effusion [20,21]. The underlying mechanisms that caused pericardial efussion was increased capillary permeability and impaired lymphatic drainage. Most possible explanation for effusions in patients with established connective tissue disorder was inflammation. In our series, one patient who presented with pericardial efussion was found to have hypothyroidism after thorough laboratory evaluation. Three patients had a history of connective tissue disorder: one of them with established systemic lupus eritematozus (SLE), and the other two patients with RA. With the aim of detecting specific etiology in patients with established connective tissue disorder anti nuclear antibody (ANA), rheumatoid factor (RF) and thyroid stimulating hormone (TSH) were rated as practical and cost effective measures. In ten patients, we could not find the specific etiology. Four out of 10 patients were previously hospitalized for urosepsis and multiple organ failure in intensive care units. All of them died during their routine follow ups. Of our 6 patients, none of them experienced a recurrence of their pericardial effusion.

In conclusion, pericardiocentesis is accepted as a gold standard method not only for accurate diagnosis of etiology, but it also plays a crucial role for the prompt management of cardiac tamponade. In patients with severe pericardial effusion who do not respond to empiric therapies, further analysis is indicated. Detailed history, physical examination and pericardiocentesis are mandatory for accurate diagnosis and choosing necessary treatment modalities.

Conflict of interest: None declared

REFERENCES

1. Alcan KE, Zabetakis PM, Marino ND, et al. Management of acute cardiac tamponade by subxiphoid pericardiotomy. JAMA 1982; 247: 1143-1148.
2. Kopecky SL, Callahan JA, Tajik AJ, et al. Percutaneous pericardial catheter drainage: Report of 42 consecutive cases. Am J Cardiol 1986; 58: 633-635.
3. Spodick DH. Pericardial diseases. In: Braunwald E, Zippes DP, Libby P, editors. Heart Disease. 6th ed. Philadelphia, London, Toronto, Montreal Sydney, Tokyo,: W.B. Saunders; 2001. p. 1823-1876.
4. Zayas R, Anguita M, Torres F, et al. Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. Am J Cardiol 1995;75:378-382.
5. Zayas R, Anguita M, Torres F, et al. Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. Am J Cardiol 1995;75:378-382.
6. Fowler NO. Cardiac tamponade a clinical or echocardiographic diagnosis. Circulation 1993; 87: 738-741.
7. Spodick DH. Physiology of the normal pericardium: Functions of the pericardium. Decker; 1997:15-26.Spodick DH.(ed). The pericardium. A Compherensive Textbook. New York: Marcel.
8. ESC Guidelines Guidelines on the Diagnosis and Management of Pericardial Diseases, 2004.
9. Oakley CM. Myocarditis, pericarditis, and other pericardial disease. Heart 2000;84:449-454.
10. Colombo A, Olson HG, Egan J, et al. Etiology and prognostic implications of a large pericardial effusion in men. Clin Cardiol 1988;11:389-394.
11. Corey GR, Campell PT, Van Trigt P, et al. Etiology of large pericardial Effusions. Am J Med 1993;95:209-213.
12. Sagrista- sauleda j, Merce j, Permanyer- Miralde g, et al Clinical clues to the causes of large pericardial effusion. Am J Med 2000;109:95-101.
13. Basar N, Turak O, Gürel M,et al. Pericardial effusion: etiology, diagnose and management. Düzce Medical Journal 2012;14;23-27.
14. Vaitkus PT, Herrman HC, LeWinter MM. Treatment of malignant pericardial effusion. JAMA 1994;272:59-64.
15. Wiener HG, Kristensen IB, Haubek A, et al. The diagnostic value of pericardial cytology. An analysis of 95 cases. Acta Cyto 1991;35:149-153.

16. Meyers DG, Meyers RE, Prendergast TW. The usefulness of diagnostic tests on pericardial fluid. Chest 1997;111:1213-21. 17. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. Circulation 2005;112:3608-3616.

18. Syed FF, Mayosi BM. A modern approach to tuberculous pericarditis. Prog Cardiovasc Dis 2007;50:218-236.

19. Reuter H, Burgess L, Van Vuren W, et al. Diagnosing tuberculous pericarditis. Q J Med 2006;99:827-839.

20. Kerber RE, Sherman B. Echocardiographic evaluation of pericardial effusion in myxedema. Circulation 1975;52:823-827.

21. Kabadi UM, Kumar SP. Pericardial effusion in primary hypothyroidism. Am Heart J 1990;120:1393-1395.