Corresponding author
Takeshi Saraya, MD, PhD
Department of Respiratory Medicine
Kyorin University School of Medicine
6-20-2 Shinkawa
Mitaka City, Tokyo 181-8611
Japan
Tel. +81 (0)422 44 0671
Fax: +81 (0)422 44 0671
E-mail: sara@yd5.so-net.ne.jp

The Role of Vital Signs in Predicting Cardiac Tamponade in Asymptomatic Patients with Malignancy: Associated Pericardial Effusion

Takeshi Saraya, MD, PhD*; **Saori Takata, MD; Masachika Fujiwara, MD, PhD; Manabu Ishida, MD; Miku Oda, MD; Kosuke Ohkuma, MD; Takayasu Watanabe, MD; Yukari Ogawa, MD; Naoki Tsujimoto, MD; Masaki Tamura, MD; Takuma Yokoyama, MD; Daisuke Kurai, MD, PhD; Haruyuki Ishii, MD, PhD; Hajime Takizawa, MD, PhD**

Department of Respiratory Medicine, Kyorin University School of Medicine, Mitaka City, Tokyo 181-8611, Japan

ABSTRACT

Background: Cardiac tamponade is a potentially life-threatening complication in patients with advanced lung cancer or other metastatic malignant diseases. However, few reports described how to assess the risk for developing cardiac tamponade in asymptomatic patients with pericardial effusion.

Methods: The medical records of all patients with malignancy-associated cardiac tamponade diagnosed between April 2006 and June 2012 at Kyorin Hospital were retrospectively reviewed. This study mainly focused on the correlation between the duration between the first recognition of pericardial effusion on computed tomography and cardiac tamponade diagnosis and the vital signs at each point.

Results: We identified 17 patients with malignancy-associated cardiac tamponade, mainly due to lung cancer (n=11, adenocarcinoma; n=1, non-small cell carcinoma; n=1, large cell neuroendocrine carcinoma; n=1, small cell carcinoma; and n=1, squamous cell carcinoma) followed by malignant mesothelioma (n=1), and an unknown cause (n=1). Among 17 patients with cardiac tamponade, the systolic blood pressure at the time of malignancy diagnosis was significantly higher than that at the onset of cardiac tamponade (average±SD, 115±13 *vs* 95±25 mm Hg; *p*=0.014), whereas heart rate (HR) and cardiothoracic ratio (CTR) determined on chest radiography were significantly higher at the onset of cardiac tamponade (HR, 84±15 bpm *vs* 111±30; *p*<0.001) (CTR, 49±7% *vs* 71±4.9; *p*=0.001). The correlation coefficient between the days from the first recognition of pericardial effusion on thoracic computed tomography to cardiac tamponade diagnosis and the gap of vital signs at each point such as ΔHR (r=−0.422, *p*=0.345) and ΔCTR (r=−0.212, *p*=0.647) was not statistically significant.

Conclusion: This preliminary study demonstrated that increased HR and CTR are essential signs for predicting malignancy-associated cardiac tamponade.

KEYWORDS: Vital signs; Cardiac tamponade; Malignancy; Lung cancer; Malignancy-associated pericardial effusion.

INTRODUCTION

Malignancy-associated pericardial effusion (MPCE) is generally caused by lung cancer, breast cancer, leukemia, and lymphomas.[1,2] MPCE most often provokes cardiac tamponade in the terminal stage, and early recognition and successful intervention could prolong life in a significant number of patients. However, no studies have been reported regarding the consideration of these markers, particularly focusing on the vital signs of asymptomatic patients with MPCE, to prevent delay in diagnosis of cardiac tamponade. We retrospectively reviewed the medical records of 17 patients with cardiac tamponade, focusing on the patient's vital signs.

MATERIALS AND METHODS

This retrospective study assessed 17 consecutive patients who were diagnosed with malignancy-associated cardiac tamponade. All patients were referred to the Pulmonary Disease Center in our hospital in Mitaka City, Tokyo, Japan, between April 2006 and June 2012. To be enrolled in the study, patients should have undergone surgical procedures such as pericardial drainage or fenestration, and/or pulsus paradoxus, as well as autopsy cases. Pulsus paradoxus is defined as a decrease in systolic blood pressure (SBP) greater than 10 mm Hg with inspiration. Vital signs such as heart rate (HR), SBP, diastolic blood pressure, pulse pressure, and cardiothoracic ratio (CTR) determined on chest radiography were assessed at the time of the diagnosis of malignancy or cardiac tamponade and the time of the first recognition of pericardial effusion on computed tomography (CT), if the data are available. ΔHR and ΔCTR were defined as absolute value for each timing between the first recognition of pericardial effusion on CT and cardiac tamponade diagnosis. This study additionally focused on seven patients with MPCE who successfully observed the process of cardiac tamponade from the phase of first recognition of pericardial effusion. In the seven patients, we evaluated the relevance between the vital signs such as ΔHR and ΔCTR. The Kaplan–Meier overall survival curve was also evaluated in 17 cases after diagnosis with cardiac tamponade.

STATISTICAL ANALYSIS

Data were statistically analyzed using the Pearson chi-square or Mann–Whitney test and SPSS version 19. Statistical significance was defined as a $p<0.05$ on paired two-sided tests.

RESULTS

Baseline Patient and Disease Characteristics

We enrolled 17 patients with cardiac tamponade, and their baseline characteristics are shown in Table 1. Age ranged from 33 to 75 years (mean±SD, 63±11 years), and female to male ratio was 14:3. The underlying diseases consisted of lung cancer (n=11, adenocarcinoma; n=1, non-small cell carcinoma; n=1, large cell neuroendocrine carcinoma; n=1, small cell carcinoma;

and n=1, squamous cell carcinoma) followed by malignant mesothelioma (n=1), and unknown cause (n=1) (Tables 1 and 2). In the present study, the number of patients in each diagnostic method was 9,4,1,1,1, and 1 for pericardial drainage, pericardial fenestration, pericardial drainage plus pulsus paradoxus, pericardial fenestration plus pulsus paradoxus, pulsus paradoxus, and autopsy, respectively. In the 17 patients, the length of time from the diagnosis of malignancy to cardiac tamponade ranged from 1 to 1970 days (median, 22 days). Among them, the length of time between the recognition of pericardial effusion on thoracic CT and cardiac tamponade was successfully assessed in 7 patients, ranging from 4 to 150 days with a median of 44 days.

Comparison of Vital Signs at the Time of Malignancy Diagnosis and at the Onset of Cardiac Tamponade

As shown in Table 3, the vital signs at the time of malignancy diagnosis and at the onset of cardiac tamponade in the 17 patients were compared. The SBP at the time of malignancy diagnosis was significantly higher than that at the onset of cardiac tamponade (average±SD, 115±13 *vs* 95±25 mm Hg; $p=0.014$),, whereas HR and CTR determined on chest radiography were significantly higher at the onset of cardiac tamponade (HR, 84±15 bpm *vs* 111±30, $p<0.001$) (CTR, 49±7 % *vs* 71±4.9 %; $p=0.001$).

Kaplan–Meier Overall Survival Curve for All 17 Patients After Cardiac Tamponade Diagnosis

In this study, one patient was lost to follow up, three patients survived, and the remaining patients died as shown in the Kaplan-Meier overall survival curve for all 17 patients after cardiac tamponade diagnosis (Figure 1). The median overall survival time was 51 days.

Relevance Between the Vital Signs of the 7 Patients and the Length of Time from the First Recognition of Pericardial Effusion on Thoracic Ct to Cardiac Tamponade Diagnosis

Among 17 patients with cardiac tamponade, only 7 patients were successfully observed the generating process of cardiac tamponade from the phase at first recognition of pericardial effusion on thoracic CT. The correlation coefficient between the

Age (mean±SD)		63±11
Sex	M/F	14/3
Histology	Adenocarcinoma	11
	Squamous cell carcinoma	1
	LCNEC	1
	NSCLC	1
	SCLC	1
	Malignant mesothelioma	1
	Unknown	1

LCNEC: Large-cell neuroendocrine carcinoma; NSCLC: Non-small cell lung cancer; SCLC: S mall Cell Lung Cancer

Table 1: Baseline patient and disease characteristics.

Case	Age	Sex	Histology	EGFR mutation	Diagnostic methods (ope/autopsy/pulsus paradoxus)	DOT from the diagnosis of malignancy to CT	DOT from the recognition of PE to CT	Additional therapy
1	68	M	NSCLC	NE	Pericardialdrainage	1	NA	Chemo
2	69	M	NSCLC(adeno)	–	Pericardialdrainage	1970	73	None
3	44	F	NSCLC(adeno)	–	–/–/pulsusparadoxus(10mmHg)	1	NA	Chemo
4	66	M	NSCLC(adeno)	NE	–/autopsy/N.E	298	4	None
5	60	F	NSCLC(adeno)	L858R	Pericardialfenestration/–/pulsusparadoxus(18mmHg)	2	NA	Chemo
6	68	M	Mesothelioma	NE	Pericardialdrainage/–/NE	467	NA	Chemo
7	67	F	NSCLC(adeno)	NE	Pericardialdrainage/–/NE	40	NA	Chemo
8	75	M	NSCLC(adeno)	NE	Pericardialfenestration/–/NE	20	18	Chemo
9	57	M	NSCLC(adeno)	NE	Pericardialdrainage	130	17	None
10	33	M	NSCLC(adeno)	NE	Pericardialfenestration/–/NE	164	150	None
11	72	M	NSCLC(adeno)	NE	Pericardialdrainage	294	91	None
12	56	M	NSCLC(adeno)	NE	Pericardialdrainage	2	NA	None
13	74	M	NSCLC(Sq)	NE	Pericardialfenestration/–/NE	108	44	Chemo
14	63	M	NSCLC(adeno)	-	Pericardialdrainage	1	NA	Chemo
15	61	M	SCLC	NE	Pericardialfenestration/–/NE	22	NA	Radiation
16	72	M	Unknown	NE	Pericardialdrainage/–/pulsusparadoxus(10mmHg)	1	NA	None
17	74	M	LCNEC	NE	Pericardialdrainage	18	NA	None

adeno: adenocarcinoma; CT: Cardiac Tamponade; Chemo: Chemotherapy; EGFR: Epidermal Growth Factor Receptor; DOT: Duration of Time; LCNEC: large-cell neuro endocrine carcinoma; NE: Not Examined; NA: Not Available; NSCLC: Non-small cell lung cancer; ope: operation; PE: Pericardial Effusion; SCLC: Small Cell Lung Cancer; Sq: Squamous carcinoma.

Table 2: Characteristics of patients with cardiac tamponade.

	At malignancy diagnosis	At the onset of cardiac tamponade	p value
SBP	115±13	95±25	$p=0.014$*
DBP	69±9	64±21	$p=0.12$
HR	84±15	111±30	$p<0.001$***
Pulse pressure	44±13	35±13	$p=0.08$
CTR	49±7	71±4.9	$p=0.001$***

CTR: Cardiothoracic ratio; DBP: Diastolic Blood Pressure; HR: Heart Rate; SBP: Systolic Blood Pressure

Table 3: Comparison of vital signs at the time of malignancy diagnosis and at the onset of cardiac tamponade in 17 patients.
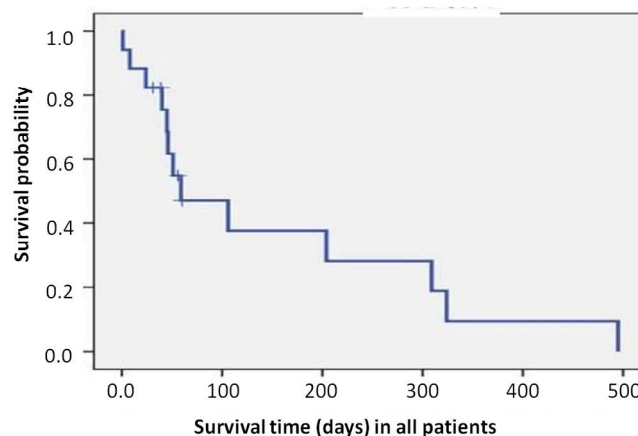

Figure 1: Kaplan–Meier overall survival curve for 17 patients after cardiac tamponade diagnosis.
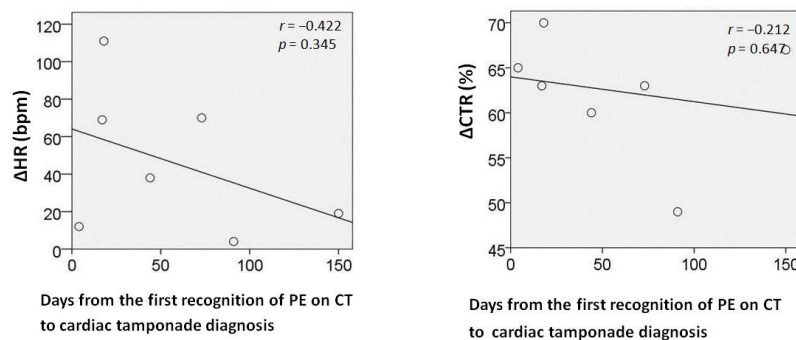
Figure 2: Relevance between the ΔHR or ΔCTR and the length of time from the first recognition of pericardial effusion to cardiac tamponade diagnosis in seven patients with cardiac tamponade

days from the first recognition of pericardial effusion to cardiac tamponade diagnosis and the gap of vital signs such as ΔHR ($r=-0.422$, $p=0.345$) and ΔCTR ($r=-0.212$, $p=0.647$) was not significant (Figure 2).

DISCUSSION

Lung cancer is one of the most common causes of MPCE, with effusion volume as less as 50 mL often detected incidentally on CT.[3] However, few reports described how to assess the risk for developing cardiac tamponade or to evaluate the vital signs in their management, particularly in patients with asymptomatic MPCE.[4] The present study would be the first to investigate the correlation between the vital signs and the duration between recognition of pericardial effusion to cardiac tamponade (Figure 2). Roy et al[4] described that pulsus paradoxus and tachycardia showed high sensitivity for cardiac tamponade at 82% and 77%, respectively. Similarly, our study showed that HR at the onset of cardiac tamponade was significantly higher than that at the diagnosis of malignancy (Table 3), similar to the trend observed for CTR on chest radiography and SBP. We clinically judged and included one patient (case 4) as cardiac tamponade who had only pulsus paradoxus, and two of three patients with pulsus paradoxus (cases 5 and 16) required pericardial drainage or fenestration, suggesting that this sign still appears to be one of the most reliable markers for surgical treatment.

We also found that ΔHR might be a sensitive marker for detecting cardiac tamponade after recognition of asymptomatic MPCE, but this was not statistically significant, which was probably because of the following limitations: 1) this study is a retrospective study, 2) sample size of patients with cardiac tamponade was small, 3) there was no clear consensus among cardiovascular surgeons on performing surgical intervention, and 4) cardiac tamponade is a first manifestation of the malignant disease (case 1,3,5,12, 14, and 16).

This study re-confirmed the fact that lung adenocarcinoma is the most common cause of cardiac tamponade as described in previous reports,[2,5] and the median survival rate in patients with cardiac tamponade was significantly lower (51 days) than that in patients with stage IV non-small cell lung cancer (4

to 6 months).[6] In this regard, early recognition and successful intervention could prolong life for a significant number of patients.

In conclusion, our study showed the importance of assessing vital signs such as SBP or HR even in patients with asymptomatic MPCE in their management, which will ensure intervention within time.

CONFLICTS OF INTEREST: None.

CONSENT

Authors obtain written informed consent from the patient for submission of this manuscript for publication.

REFERENCE

1. Burazor I, Imazio M, Markel G, Adler Y. Malignant pericardial effusion. *Cardiology*. 2013; 124(4): 224-232. doi: 10.1159/000348559

2. Wilkes JD, Fidias P, Vaickus L, Perez RP**.** Malignancy-related pericardial effusion. 127 cases from the Roswell Park Cancer Institute. *Cancer*. 1995; 76(8): 1377-1387. doi: 0.1002/1097-0142(19951015)76:8<1377::AID-CNCR2820760813>3.0.CO;2-M

3. Shepherd FA**.** Malignant pericardial effusion. *Curr Opin Oncol*. 1997; 9(2): 170-174. Web site. http://journals.lww.com/co-oncology/Abstract/1997/03000/Malignant_pericardial_effusion.11.aspx. Accessed May 11, 2016

4. Roy CL, Minor MA, Brookhart MA, Choudhry NK**.** Does this patient with a pericardial effusion have cardiac tamponade? *JAMA*. 2007; 297(16): 1810-1818. doi: 10.1001/jama.297.16.1810

5. Okamoto H, Shinkai T, Yamakido M, Saijo N**.** Cardiac tamponade caused by primary lung cancer and the management of pericardial effusion. *Cancer*. 1993; 71(1): 93-98. doi: 10.1002/1097-0142(19930101)71:1<93::AID-CNCR28207

10115>3.0.CO;2-R

6. Cetin K, Ettinger DS, Hei YJ, O'Malley CD. Survival by histologic subtype in stage IV nonsmall cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. *Clin Epidemiol*. 2011; 3: 139-148. doi: 10.2147/CLEP. S17191