Hospital Volume and Cardiac Complications of Endomyocardial Biopsy: A Retrospective Cohort Study of 9508 Adult Patients Using a Nationwide Inpatient Database in Japan

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ABSTRACT

Background: Recent research on complications with endomyocardial biopsy (EMB) has been based on single-center or 2-center studies in high-volume cardiovascular centers. No study has examined the association between hospital volume and the complication rate after EMB.

Hypothesis: Hospital volume is inversely associated with cardiac complication rate after EMB.

Methods: Using the Diagnosis Procedure Combination database in Japan, we identified inpatients aged ≥ 20 years who underwent EMB under fluoroscopic guidance. We assessed cardiac complications requiring the following urgent procedures on the day of EMB or the day after: pericardiocentesis, surgical repair, and temporary pacing.

Results: Among 9508 eligible patients in 491 hospitals (male, 68%; mean age, 57.0 years), dilated cardiomyopathy was the most frequently diagnosed condition (35.4%). Twenty-four patients (0.25%) required pericardiocentesis on the day of EMB. Three patients (0.03%) underwent surgical repair on the day of EMB or the day after. Sixty-three patients (0.70%) required temporary pacing on the day of EMB. Higher hospital volume was associated with lower rates of pericardiocentesis (low volume, 0.4%; medium volume, 0.2%; high volume, 0.1%; P for the trend test, 0.019) and temporary pacing (low volume, 1.0%; medium volume, 0.7%; high volume, 0.2%; P for the trend test, < 0.001). In a multivariable logistic regression analysis, high hospital volume was significantly associated with a lower rate of the composite outcome of the procedures (reference, low volume; adjusted odds ratio, 0.22; 95% confidence interval, 0.08–0.62, $P = 0.004$).

Conclusions: Serious cardiac complications of EMB were rare, but higher hospital volume was associated with lower complication rate.

Introduction

Endomyocardial biopsy (EMB) is an established diagnostic procedure for evaluating unexplained cardiomyopathy and monitoring transplant rejection.^{1,2} Since nonsurgical EMB techniques were introduced into clinical practice and advanced in the 1960s and 1970s,^{3–6} EMB has been widely

performed; this is because noninvasive examinations, such as cardiovascular imaging and cardiac biomarkers, are not sufficiently specific to diagnose several cardiac diseases, such as myocarditis and infiltrative cardiomyopathy.^{1,2}

Owing to its invasive nature, EMB may cause serious cardiac complications, such as ventricular perforation with cardiac tamponade and complete atrioventricular block. Early studies published in the 1990s showed that the rates of major cardiac complications associated with EMB were $< 1\%$.^{7–11} Recent studies published in the 2000s to 2010s likewise indicated that the complication rates were low.^{12–16} However, those studies were based on single-center or

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2-center experiences in high-volume cardiovascular centers and may not be generalizable to other hospitals. Multicenter studies (> 2 centers) on EMB complications are limited to 2 questionnaire-based surveys published before 2000.^{17,18} Thus, the risk of EMB in current practice has yet to be examined in a large-scale, multicenter study.

The Scientific Statement from the American Heart Association (AHA), American College of Cardiology Foundation (ACCF), and European Society of Cardiology (ESC) recommends that “if a patient with an indication for EMB presents at a medical center where expertise in EMB and cardiac pathology is unavailable, transfer of the patient to a medical center with such experience should be seriously considered.”² This recommendation is appropriate for heart transplant patients, because they generally need to be managed medically and surgically by heart transplant specialists and undergo repeated EMB procedures to assess transplant rejection. However, this recommendation may not be applicable to all patients requiring EMB. Many patients with unexplained cardiomyopathy are indicated for an EMB, but the number of cardiovascular centers with expertise in this procedure is very limited. If EMB candidates were routinely transferred to high-volume centers, the resources of such centers would be overwhelmed, thereby rendering EMB procedures even less accessible. Although the associations between hospital volume and outcome have been shown for many surgical and nonsurgical procedures in previous studies,^{19,20} no study has examined the association between hospital volume and the complication rate after EMB.

To determine the current situation in this regard, it is essential to verify the complication rates of EMB in a nationwide setting. We hypothesized that hospital volume was inversely associated with the complication rate after EMB. The purpose of the present study was to evaluate the cardiac complications of EMB and examine the association between the hospital volume and cardiac complication rate of EMB, using a national inpatient database in Japan.

Methods

Data Source

The data in this study were extracted from the Diagnosis Procedure Combination (DPC) database, the details of which are explained elsewhere.²¹ The database includes information for approximately 18 million inpatients over the 33 months between July 1, 2010, and March 31, 2013, from approximately 1000 hospitals in Japan. These account for approximately 50% of all inpatient admissions to acute-care hospitals in the country. The present study was approved by the institutional review board at The University of Tokyo. Because all the data were anonymized, the requirement for informed consent in this study was waived.

The DPC database includes the following data: patient age and sex, height and weight, use or nonuse of an ambulance for admission, diagnoses recorded using the *International Classification of Diseases, Tenth Revision* (ICD-10) codes and text data written in the Japanese language, drugs and medical devices, diagnostic and therapeutic procedures, length of stay, discharge status, and unique hospital identifiers.

Study Population and Data

The study population in this study consisted of adult inpatients aged ≥ 20 years who underwent an EMB procedure under fluoroscopic guidance between July 1, 2010, and March 31, 2013. We excluded patients who underwent an EMB procedure ≥ 2 times during index hospitalization. Baseline variables were age, sex, body mass index, ambulance use or nonuse, Charlson Comorbidity Index (calculated using ICD-10 codes of comorbidities),²² hospital volume, and type of hospital (academic or nonacademic). Hospital volume was defined as the annual number of patients undergoing an EMB procedure at each hospital and categorized into tertile (low-volume, medium-volume, and high-volume) groups, with approximately equal numbers of patients in each group. We also identified a diagnosis of the cardiac disorder at discharge for each patient using the ICD-10 codes. To optimize the accuracy of the recorded diagnoses in the DPC system, attending physicians are obliged to record the diagnoses and comorbidities with reference to medical charts at discharge. However, if patients were discharged before the results of EMB became available, the diagnoses were based on the results of examinations other than EMB.

Outcome Definitions

In this study, we identified the occurrence of cardiac complications by means of urgent procedures required on the day of EMB or the day after. The outcomes were pericardiocentesis and surgical repair required on the day of EMB or the day after, and temporary pacing required on the day of EMB. We defined the composite outcome as being pericardiocentesis, surgical repair, and temporary pacing. We also examined in-hospital death.

Statistical Analysis

Categorical variables are presented as numbers and proportions. Continuous variables are presented as mean $\pm$ SD if they followed a normal distribution, otherwise as the median and interquartile range (IQR).

To assess the association between hospital volume and complication rates of EMB, we first examined the trend in the rates of pericardiocentesis and temporary pacing according to hospital-volume category using the Cochran-Armitage test. Second, we performed a multivariable logistic regression analysis of the composite outcome with adjustments for baseline variables and diagnoses at discharge. We fitted the regression model with a generalized estimating equation to take clustering within hospitals into consideration.²³ We then determined odds ratios (OR) and 95% confidence intervals (CI) for each covariate. All hypothesis tests had a 2-sided significance level of 0.05. We conducted all statistical analyses using SPSS version 22 (IBM Corp., Armonk, NY).

Results

We identified 9618 inpatients aged ≥ 20 years who underwent an EMB procedure. We excluded 110 patients who underwent an EMB procedure ≥ 2 times during the index

hospitalization. Thus, the study population was the remaining 9508 eligible patients in 491 hospitals (male, 68%; mean age, 57.0 ± 14.7 years). The composite outcome occurred in 87 patients (0.9%). Twenty-four (0.25%) patients required pericardiocentesis on the day of EMB, though no patients required it the day after. Two (0.02%) patients underwent surgical repair on the day of EMB, and 1 (0.01%) did so the day after. Temporary pacing was required by 63 (0.70%) patients on the day of EMB. One patient with myocarditis died on the day of EMB. The overall in-hospital mortality was 1.4% ($n = 132$), and the median length of stay was 17 days (IQR, 6–29 days). The 491 hospitals that performed EMB were classified into 101 academic and 390 nonacademic hospitals. We also categorized the 491 hospitals into 413 low-volume, 59 medium-volume, and 19 high-volume hospitals. Table 1 shows the baseline characteristics and outcome of the 9508 eligible patients.

Table 2 shows the diagnoses of cardiac disorders at discharge in the study population. Dilated cardiomyopathy was the most frequently diagnosed condition, accounting for approximately one-third of the patients; it was followed by hypertrophic cardiomyopathy. Sarcoidosis, amyloidosis, and myocarditis were diagnosed in < 10% of the patients. Heart transplant patients amounted to 3.6%. Patients with myocarditis had a relatively high rate of the composite outcome.

Table 3 shows detailed information about the patients requiring urgent procedures. The majority of the patients requiring urgent procedures were age ≥ 50 years. Among such subjects, 1 patient requiring pericardiocentesis, 1 patient undergoing surgical repair, and 7 patients requiring temporary pacing died during hospitalization.

The rates of pericardiocentesis were 0.4%, 0.2%, and 0.1% in the low-volume, medium-volume, and high-volume hospitals, respectively. The Cochran-Armitage test showed a significant trend in the rate of pericardiocentesis according to hospital volume category ($P = 0.019$). The rates of temporary pacing were 1.0%, 0.7%, and 0.2% in the low-volume, medium-volume, and high-volume hospitals, respectively. The Cochran-Armitage test showed a significant trend in the rate of temporary pacing according to hospital volume category ($P < 0.001$).

Table 4 shows the results of a multivariable logistic regression analysis for the composite outcome. The results showed that higher age, female sex, ambulance use for admission, and a diagnosis of myocarditis were significantly associated with a higher rate of the composite outcome, whereas high hospital volume and Charlson Comorbidity Index were significantly associated with a lower rate of the composite outcome.

Discussion

This retrospective cohort study investigated the rates of cardiac complications associated with EMB using a large-scale nationwide inpatient database in Japan. Our results show that the rates of serious cardiac complications requiring urgent procedures were low—< 1%—including pericardiocentesis (0.25%) and surgical repair (0.03%). This study found that higher hospital volume was significantly associated with lower rates of cardiac complications.

Table 1. Baseline Characteristics and Outcome of the 9508 Eligible Patients

Factor	No. (%)	Composite Outcome, No. of events (%)
Age, y		
20–29	426 (4.5)	3 (0.7)
30–39	987 (10.4)	8 (0.8)
40–49	1474 (15.5)	8 (0.5)
50–59	1988 (20.9)	18 (0.9)
60–69	2531 (26.6)	18 (0.7)
70–79	1755 (18.5)	21 (1.2)
≥ 80	347 (3.6)	11 (3.2)
Sex		
M	6463 (68.0)	47 (0.7)
F	3045 (32.0)	40 (1.3)
BMI, kg/m ²		
< 18.5	973 (10.2)	6 (0.6)
18.5–22.9	3543 (37.3)	32 (0.9)
23.0–24.9	1713 (18.0)	22 (1.3)
25.0–29.9	2062 (21.7)	18 (0.9)
≥ 30.0	864 (9.1)	4 (0.5)
Missing	353 (3.7)	5 (1.4)
Ambulance		
Use	1480 (15.6)	26 (1.8)
Nonuse	8028 (84.4)	61 (0.8)
CCI		
0	1304 (13.7)	25 (1.9)
1	4842 (50.9)	37 (0.8)
2	1990 (20.9)	18 (0.9)
≥ 3	1372 (14.4)	7 (0.5)
Type of hospital		
Academic	5046 (53.1)	36 (0.7)
Nonacademic	4462 (46.9)	51 (1.1)
Hospital volume, per year		
Low (≤ 14)	3510 (36.9)	47 (1.3)
Medium (15–36)	3141 (33.0)	31 (1.0)
High (≥ 37)	2857 (30.0)	9 (0.3)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; F, female; M, male.

Table 2. Diagnoses of Cardiac Disorders at Discharge and Outcome (N = 9508)

Diagnosis	ICD-10 Code	n (%)	Composite Outcome, No. of events (%)
Dilated cardiomyopathy	I42.0	3365 (35.4)	16 (0.5)
Hypertrophic cardiomyopathy	I42.1, I42.2	1110 (11.7)	5 (0.5)
Sarcoidosis	D86.x	690 (7.3)	11 (1.6)
Amyloidosis	E85.x, I43.1	403 (4.2)	5 (1.2)
Heart transplant state	T86.2, T86.3, Z94.1, Z94.3	341 (3.6)	0 (0.0)
Myocarditis	I40.x, I41.x	320 (3.4)	16 (5.0)
ARVC ^a	I42.8	70 (0.7)	0 (0.0)
Ischemic cardiomyopathy	I25.5	67 (0.7)	1 (1.5)
Takotsubo cardiomyopathy ^a	I51.8	58 (0.6)	2 (3.4)
Drug-induced cardiomyopathy	I42.7	36 (0.4)	0 (0.0)
Peripartum cardiomyopathy	O90.3	35 (0.4)	0 (0.0)
Alcoholic cardiomyopathy	I42.6	34 (0.4)	0 (0.0)
Muscular dystrophy	G71.0	24 (0.3)	0 (0.0)
Mitochondrial encephalomyopathy	E88.8, G71.3	24 (0.3)	0 (0.0)
Fabry disease	E75.2	24 (0.3)	0 (0.0)
Cardiac tumor	D15.1, D48.7	22 (0.2)	0 (0.0)
Hemochromatosis	E83.1	5 (0.1)	1 (20.0)
Other cardiomyopathy	I11.x, I13.x, I42.3, I42.4, I42.5, I42.9, I43.0, I43.2, I43.8	811 (8.5)	6 (0.7)
NA ^b	—	2069 (21.8)	24 (1.2)

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD-10, *International Classification of Diseases, Tenth Revision*; NA, not available.

^aBecause there are no specific ICD-10 codes for ARVC or Takotsubo cardiomyopathy, the 2 diagnoses were determined by using text data written in Japanese in combination with the relevant ICD-10 codes. ^bData about the specific diagnosis of cardiac disorder were not available in the database.

In 1998, a nationwide questionnaire-based survey in Japan (19 964 patients in 134 centers) found that the rate of ventricular perforation was 0.7% (total, n = 147; right ventricle [RV], n = 115; left ventricle [LV], n = 31) with a mortality of 0.05% (n = 10).¹⁷ However, the results from that study may not be applicable to current clinical practices because EMB was not as widely performed then as it is today. Since that questionnaire-based study was published, no large-scale, multicenter study (> 2 centers) on EMB has been conducted. In the 2000s and 2010s, the results of several single-center or 2-center studies in high-volume hospitals suggested that the rates of major complications were low if the procedure was performed by experienced physicians.^{12–16} In 2008, Holzmann et al reported that major cardiac complications occurred in 3 cases (0.1%) among 3048 RV EMB procedures via the femoral vein in 2415 patients (cardiac tamponade requiring pericardiocentesis, n = 2; complete atrioventricular block requiring permanent pacemaker, n = 1).¹² In 2010, Yilmaz et al investigated the risk of complications in 622 LV and 490 RV EMB procedures in 755 patients; they found that the rates of cardiac tamponade with pericardiocentesis were 0.32% (n = 2) and 0.82% (n = 4) for LV and RV EMB, respectively.¹³

In 2011, Paul et al reported that cardiac tamponade with pericardiocentesis occurred in 8 (0.06%) of 2803 EMB procedures in 753 patients, which included 161 patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and 271 heart transplant patients.¹⁴ Saraiva et al reported that cardiac perforation with tamponade occurred in 1 case (0.05%) among 2217 EMB procedures in 175 heart transplant patients.¹⁵ In 2013, Chimenti et al compared the risk of major complications between 3549 LV and 3068 RV EMB procedures; they found that the incidences of cardiac tamponade with pericardiocentesis were 0.08% (n = 3) and 0.29% (n = 9) for LV and RV EMB, respectively.¹⁶ In those recent observational studies, no patient died or underwent urgent cardiac surgery owing to EMB-related complications, although the number of patients receiving cardiac tamponade with pericardiocentesis was small (n = 1–12).

The present study included 9508 patients who underwent EMB in 491 hospitals and identified 24 pericardiocentesis cases, 3 surgical-repair cases, and 63 temporary-pacing cases. In this study, 1 patient with myocarditis died on the day of EMB, though the association between EMB and death was unclear. The proportion of heart transplant patients was

Table 3. Patients Undergoing Urgent Procedures for EMB-Related Cardiac Complications

	Pericardiocentesis (n = 24)	Surgical Repair (n = 3)	Temporary Pacing (n = 63)
Age, y			
20–29	2 (8.3)	0 (0.0)	2 (3.2)
30–39	1 (4.2)	0 (0.0)	7 (11.1)
40–49	1 (4.2)	0 (0.0)	7 (11.1)
50–59	3 (12.5)	0 (0.0)	15 (23.8)
60–69	7 (29.2)	1 (33.3)	10 (15.9)
70–79	8 (33.3)	0 (0.0)	14 (22.2)
≥ 80	2 (8.3)	2 (66.7)	8 (12.7)
Sex			
M	11 (45.8)	1 (33.3)	37 (58.7)
F	13 (54.2)	2 (66.7)	26 (41.3)
Diagnosis at discharge			
Dilated cardiomyopathy	3 (12.5)	0 (0.0)	13 (20.6)
Hypertrophic cardiomyopathy	1 (4.2)	1 (33.3)	3 (4.8)
Sarcoidosis	3 (12.5)	0 (0.0)	8 (12.7)
Amyloidosis	2 (8.3)	0 (0.0)	3 (4.8)
Myocarditis	3 (12.5)	0 (0.0)	15 (23.8)
Ischemic cardiomyopathy	0 (0.0)	0 (0.0)	1 (1.6)
Takotsubo cardiomyopathy	0 (0.0)	0 (0.0)	2 (3.2)
Hemochromatosis	1 (4.2)	0 (0.0)	0 (0.0)
Other cardiomyopathy	1 (4.2)	0 (0.0)	5 (7.9)
NA ^a	11 (45.8)	2 (66.7)	13 (20.6)
Type of hospital			
Academic	10 (41.7)	2 (66.7)	25 (39.7)
Nonacademic	14 (58.3)	1 (33.3)	38 (60.3)
Hospital volume, per year			
Low (≤ 14)	14 (58.3)	1 (33.3)	34 (54.0)
Medium (15–36)	7 (29.2)	2 (66.7)	23 (36.5)
High (≥ 37)	3 (12.5)	0 (0.0)	6 (9.5)
In-hospital mortality	1 (4.2)	1 (33.3)	7 (11.1)
Abbreviations: EMB, endomyocardial biopsy; F, female; M, male. Data are presented as n (%).			
^a Data about the specific diagnosis of cardiac disorder were not available in the database.			

Table 4. Multivariable Logistic Regression Analysis for the Composite Outcome

		OR	95% CI	P Value
Age, by 10-year increase		1.29	1.09–1.54	0.003
F sex	Ref: M sex	1.62	1.03–2.53	0.035
BMI, kg/m ²	< 18.5	Ref		
	18.5–22.9	1.47	0.64–3.37	0.365
	23.0–24.9	2.25	0.91–5.56	0.079
	25.0–29.9	1.67	0.67–4.13	0.267
	≥ 30.0	1.18	0.33–4.19	0.794
	Missing	1.62	0.48–5.47	0.437
Ambulance use	Ref: nonuse	1.80	1.08–3.02	0.025
CCI	0	Ref		
	1	0.41	0.23–0.73	0.002
	2	0.45	0.24–0.84	0.013
	≥ 3	0.24	0.09–0.59	0.002
Academic hospital	Ref: nonacademic	1.08	0.58–2.04	0.803
Hospital volume, per year	Low (≤ 14)	Ref		
	Medium (15–36)	0.65	0.35–1.19	0.162
	High (≥ 37)	0.22	0.08–0.62	0.004
Diagnosis at discharge	Dilated cardiomyopathy	Ref		
	Hypertrophic cardiomyopathy	0.59	0.21–1.67	0.319
	Sarcoidosis	1.93	0.83–4.50	0.128
	Amyloidosis	2.03	0.70–5.86	0.189
	Myocarditis	7.27	3.44–15.37	< 0.001
	Others	1.83	0.97–3.47	0.063
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; F, female; M, male; OR, odds ratio; Ref, reference.				

small in this study, partly because heart transplantation is rarely performed in Japan owing to the severe shortage of donors. A previous study reported that only 113 heart transplants were performed in Japan for the 13-year period between 1999 and 2011.²⁴ Although the results of the present study may not be comparable with those of others because of the different definitions of complications, the rates of cardiac tamponade with pericardiocentesis we found were, at < 1%, similarly low compared with previously reported figures. This multicenter study suggested that serious cardiac complications of EMB were rare, but some patients with complications required pericardiocentesis and surgical repair. Thus, rapid pericardiocentesis and surgical repair

for ventricular perforation with cardiac tamponade should be available at hospitals that perform EMB.

The present study found that higher hospital volume was associated with lower rates of serious cardiac complications after EMB. In terms of preventing complications, therefore, patients with an indication for EMB should, where possible, be transferred to a high-volume hospital with the appropriate expertise. Our findings may support the recommendation of the AHA/ACCF/ESC Scientific Statement.² However, because in the present study high-volume hospitals were limited to 3.9% (19/491) of all hospitals performing EMB—and even among the low-volume hospitals the fatal complication rates were substantially low—it may be acceptable for experienced physicians to perform EMB at low-volume hospitals.

There is no specific and detailed guideline for the recommendations of EMB in Japan in the form of the AHA/ACCF/ESC Scientific Statement in Western countries.² As described in a previous study from a cardiovascular center in Japan,²⁵ EMB seems to be generally performed in Japan according to the AHA/ACCF/ESC Scientific Statement.² Thus, clinical indications for EMB in Japan ought to be similar to those in Western countries. However, several EMB cases in the present study may not necessarily have conformed to the recommendations of the Scientific Statement. For example, EMB may not always be useful in the diagnosis of hypertrophic cardiomyopathy: EMB findings are nonspecific, and a definitive diagnosis cannot be made by EMB alone.²⁵ However, hypertrophic cardiomyopathy occasionally needs to be differentiated from other cardiac disorders with LV hypertrophy, such as cardiac amyloidosis and Fabry disease. In such cases with LV hypertrophy, EMB is required for the definitive diagnosis because noninvasive examinations are not always sufficient in diagnosing several cardiac disorders. Thus, we believe that the results of the present study reflect actual practice with EMB in Japan.

The rate of the composite outcome was 5.0% (16/320) in the myocarditis group; the multivariable logistic regression analysis showed that a diagnosis of myocarditis was significantly associated with a higher rate of the composite outcome. One possible reason for this is that inflamed ventricles in myocarditis are more likely to be injured by EMB than ventricles in other cardiomyopathies. Recent studies have found that noninvasive cardiac magnetic resonance imaging displayed good diagnostic performance with myocarditis and heart failure.^{26,27} If cardiac magnetic resonance imaging is appropriately utilized, some EMB procedures may be avoided.

Study Limitations

The present study has several limitations. First, the DPC database does not include detailed information about EMB procedures, such as the site of EMB (RV or LV, or both; interventricular septum; or other places), the site of vascular access (femoral or jugular approach), and the total number of specimens extracted from the heart. Thus, it was impossible to determine whether the differences in EMB position were associated with complications. Second, the database likewise omits data about cardiac function and

morphology (e.g., electrocardiographic findings, ejection fraction, size, and ventricular wall thickness). Third, urgent procedures just after EMB may not necessarily be a direct consequence of EMB. Thus, our results may have been an overestimation of the true rates of complications. Fourth, we were unable to clarify whether the higher proportions of pericardiocentesis and temporary pacing in the low-volume hospitals were actually linked to different EMB techniques or to different management of complications. Fifth, details of the physician volume were not available for analysis due to the lack of data in the database about the physicians who performed EMB. Sixth, likewise because of data unavailability, we were unable to assess other complications of EMB, such as pericardial effusion without pericardiocentesis, cerebral or pulmonary embolization, and damage to valves or blood vessels. Seventh, although our study group is large, the sample was not randomly selected and does not represent a whole population in Japan. Finally, because of the retrospective design with the secondary use of administrative data, the diagnoses in this study were not less well validated than those in prospective studies.

Conclusion

This retrospective cohort study showed that the rates of cardiac complications requiring urgent procedures were low in patients with EMB, but pericardiocentesis and surgical repair were occasionally required for complicated cases. Our results suggested that higher hospital volume was associated with a lower complication rate.

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