Left Ventricular Apical Ballooning Due to Severe Physical Stress in Patients Admitted to the Medical ICU*

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Purpose: **We sought to assess the frequency and clinical implications of left ventricular apical ballooning (LVAB) in patients who had been admitted to the medical ICU for noncardiac physical illnesses.**

Methods: **Ninety-two consecutive patients who were admitted to the medical ICU from March to May 2003 were prospectively enrolled. Patients underwent echocardiography on the day of ICU admission, and on the third and seventh days in the hospital. LVAB was defined as symmetric severe hypokinesia or akinesia of the left ventricular wall, except for the basal part of the left ventricle, with a < 50% ejection fraction.**

Results: **Of the 92 patients, 65 (71%) were men, and they had a mean (± SD) age of 63 ± 11 years. LVAB was observed in 26 patients (28%), with a mean lowest ejection fraction of 33 ± 8% (range, 19 to 46%). Compared with the 66 patients (72%) without LVAB, those with LVAB had a higher frequency of sepsis (62% vs 14%, respectively; $p < 0.001$), a higher prevalence of hypotension on ICU admission, more frequent use of inotropic agents, and a higher frequency of cardiomegaly and pulmonary edema ($p < 0.005$ for each). Sepsis was the only variable associated with the development of LVAB (odds ratio, 9.2; 95% confidence interval, 2.4 to 35.8; $p < 0.001$). The development of Q-wave or ST-segment displacement was associated with LVAB, but the sensitivities were 12% and 19%, respectively. Serum creatine kinase level was elevated in 12 of 26 patients (46%) with LVAB. The normalization of this condition occurred in 20 of 26 patients (77%) a mean duration of 7.4 ± 5.6 days later (range, 2 to 25 days). The mean 2-month survival rate was lower in patients with LVAB than in those without (71 ± 6% vs 52 ± 10%, respectively; $p = 0.047$).**

Conclusion: **LVAB develops in a considerable number of patients who are admitted to the medical ICU, and echocardiography is useful in detecting this phenomenon.**

(CHEST 2005; 128:296–302)

Key words: critical care; echocardiography; left ventricular dysfunction; stress

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; LVAB = left ventricular apical ballooning; OR = odds ratio

A newly described heart syndrome consists of reversible left ventricular dysfunction with characteristic apical ballooning in patients without significant epicardial coronary artery stenosis.[1–3] This syndrome, also known as *takotsubo cardiomyopathy*, is believed to be associated with various clinical scenarios, especially with intense mental or emotional stress, such as that brought on by the sudden loss of family members.[4,5] Although previous investigators[3] have focused on the differential diagnosis with acute myocardial infarction and have reported excellent prognosis for patients with this syndrome, acute-phase complications such as hypotension, pulmonary congestion, and ventricular arrhythmias have also been described. Considering the fact that acute onset and aggravation of various systemic disorders, including physical problems can be a possible trig-

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Manuscript received September 30, 2004; revision accepted December 20, 2004.
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gering factor for this syndrome,[3] the development of left ventricular dysfunction with those complications is expected to affect myocardial function or recovery from critical illness, which ultimately has a tremendous prognostic impact on patients who are receiving critical care.

The evaluation of cardiac function in critically ill patients with sepsis or severe hypoxemia is one of the crucial steps for their proper management. Although the aggravation of underlying noncardiac physical disorders has been found to trigger the development of reversible myocardial contraction abnormalities,[2,3,5] the incidence or clinical significance of left ventricular apical ballooning (LVAB) in critically ill patients has not been investigated prospectively. We hypothesized that noncardiac physical illness requiring admission to a medical ICU can cause LVAB. To test this hypothesis, we performed serial echocardiographic follow-up on critically ill patients without a significant history of cardiac disorders.

Materials and Methods

Study Population

All patients admitted to the medical ICU of Asan Medical Center in Seoul, South Korea, from March 1 to May 31, 2003, were prospectively investigated. This study was approved by our institutional review boards. Patients with a medical history of any cardiac disease or a previous abnormal ECG (*ie*, pathologic Q-wave or ST-segment displacement of > 1 mm) were excluded, as were patients with a poor window for echocardiography. All patients underwent routine transthoracic echocardiography by expert sonographers on the day of ICU admission, and repeat examinations were performed on the third and seventh days. On the same days, all patients underwent recording ECGs, and blood sampling for the presence of cardiac enzymes and catecholamines. In addition, attending physicians gathered clinical information, using a standardized data form, on patient demographics, history, clinical presentation, physical findings, changes in vital signs, imaging results, details of clinical management including the use of mechanical ventilation and oxygen therapy, and patient outcomes. Sepsis, the systemic response to infection, was defined by the presence of two or more of the following conditions: (1) body temperature of > 38°C or < 36°C; (2) heart rate of > 90 beats/min; (3) respiratory rate of > 20 breaths/min or $Paco_2$ of <4.3 kPa; and (4) leukocyte count of > 120,000 cells/μL or > 10% immature (band) forms.[6] Volume resuscitation was defined as the rapid infusion of either a crystalloid or a colloid at a rate of 500 to 1,000 mL over 30 min for crystalloids or 300 to 500 mL over 30 min for colloids. Indications of volume resuscitation included central venous pressure of < 8 mm Hg, mean arterial pressure of < 65 mm Hg, and urine output of < 0.5 mL/kg/h.

Data Analysis

Echocardiograms were analyzed by two experts (J.H.P. and J.K.S.) blinded to any clinical data. Left ventricular systolic and diastolic volumes were measured using the Simpson method to calculate the ejection fraction. Typical LVAB was defined as the development of severe symmetrical hypokinesia or akinesia of the left ventricular wall, except for the basal part of the left ventricle, with a reduced ejection fraction (< 50%). Patients who showed typical LVAB by echocardiography on the first day, but who died before the follow-up study, were included in the study population only if there had been a completely normal ECG or echocardiogram performed < 3 months prior to hospital admission.

Numeric variables are expressed as the mean ± SD. The statistical analysis of differences between groups was assessed by the Student unpaired *t* test. The χ^2 test and Fisher exact test were used to compare the frequency ratios between groups. Stepwise multivariable logistic regression models were fitted using variables that were found to have marginal association with the development of LVAB ($p < 0.10$). A Kaplan-Meier analysis with log rank test was used to compare the 2-month cumulative survival rates. A probability value of < 0.05 was considered to be statistically significant.

Results

During the study period, a total of 121 patients was admitted to the medical ICU, of whom 29 were excluded from the study due to a history of underlying heart diseases, including cor pulmonale (n = 15), cardiopulmonary resuscitation on the day of hospital admission (n = 10), and poor echocardiographic window (n = 4). The remaining 92 patients had a mean age of 63 ± 11 years (age range, 29 to 85 years), and 65 (71%) were men. Hypoxia and respiratory failure, including hypercarbic respiratory failure, were the most common reasons for hospital admission (n = 46; 50%), followed by sepsis (n = 25; 27%), hemoptysis (n = 7; 7.6%), and comatose mentality (n = 6; 6.5%). The other reasons for intensive care were rhabdomyolysis, liver cirrhosis, and hyperkalemia in a patient with chronic renal failure. Echocardiography revealed typical LVAB with reduced left ventricular ejection fraction (Fig 1, 2) in 26 patients (28%).

A comparison of the clinical features of the 26 patients with typical LVAB with reduced left ventricular ejection fraction (28%) and those of the 66 patients without LVAB (72%) is summarized in Table 1. There was no significant difference in age, sex ratio, and risk factors for atherosclerosis between the groups. Sepsis was more frequently associated with LVAB ($p < 0.001$) and was the most common reason for intensive care, whereas respiratory failure was the most common reason for intensive care in the patients without LVAB. Patients with LVAB showed a higher prevalence of hypotension (systolic BP, < 90 mm Hg) on the day of ICU admission (69% vs 33%, respectively; $p < 0.001$), and acute physiology and chronic health evaluation (APACHE) III score,[7] which is an index of the severity of the underlying critical condition, was not significantly different between the groups ($p = 0.06$).

Chest radiographs showed a higher frequency of

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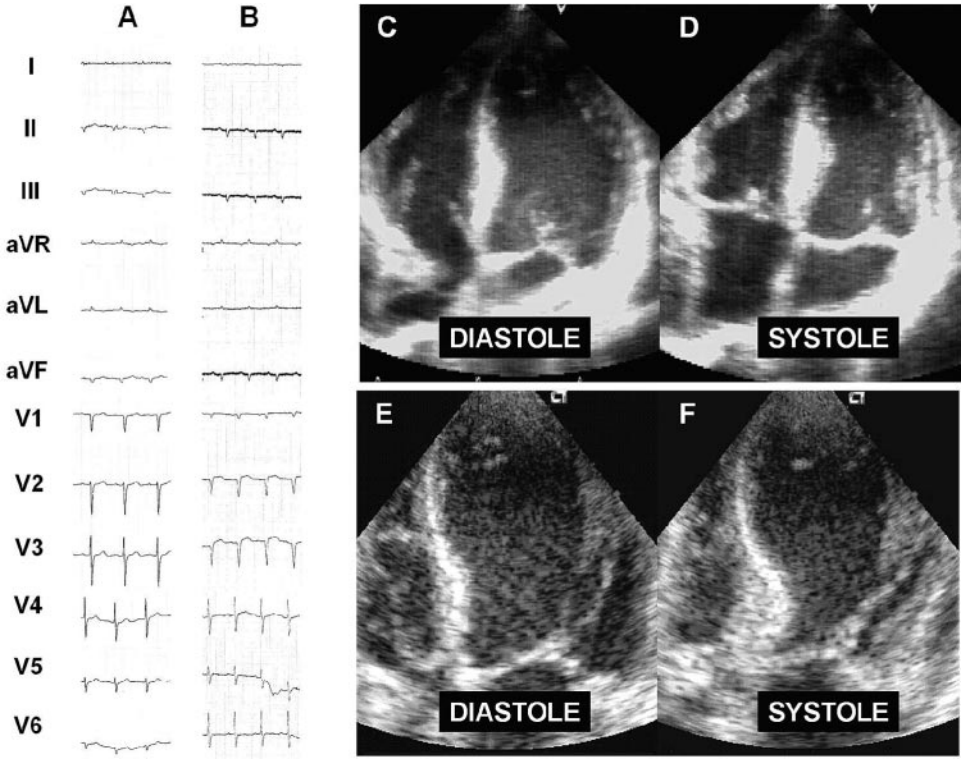

FIGURE 1. Representative ECG changes (*top left*, *A*, and *top middle left*, *B*) and echocardiograms (*top middle right*, *C*, *top right*, *D*, *bottom middle right*, *E*, and *bottom right*, *F*). The patient was a 67-year-old man who had undergone an exploratory laparotomy for advanced stomach cancer 1 month prior to hospital admission. Curative resection was not possible due to peritoneal carcinomatosis. Comprehensive preoperative evaluation of his cardiac function revealed normal ECG findings, normal left ventricular wall motion and ejection fraction (60%) on echocardiography (*top middle right*, *C*, and *top right*, *D*), and normal myocardial perfusion by stress thallium scan. The patient was readmitted to the hospital due to fever and poor oral intake, and a blood culture revealed *Escherichia coli* septicemia. His follow-up ECG (*top middle left*, *B*) showed the development of a pathologic Q wave in lead V1 to V3, with a mild elevation of cardiac enzyme levels (creatine kinase, 185 U/L; creatine kinase-MB, 5.2 U/L; troponin I, 0.8 μg/L). Follow-up echocardiography (*bottom middle right*, *E*, and *bottom right*, *F*) showed akinesia of the anterior septum, left ventricular apex, and anterolateral wall with typical LVAB and reduced ejection fraction (25%). The patient died 7 days later despite intensive supportive care.

cardiomegaly (73% vs 21%, respectively; $p < 0.001$) and pulmonary edema (96% vs 28%, respectively; $p < 0.001$) in patients with LVAB, and blood norepinephrine and C-reactive protein levels were higher in this group (Table 2). A mild elevation in serum creatine kinase levels, usually < 10 times of the upper range of normal values, was observed in 12 of 26 patients (46%) with LVAB. ECG changes were more frequent in the patients with LVAB, but the incidence of the most common change, a nonspecific minor T-wave change, was not significantly different between the groups (18% vs 31%, respectively; $p > 0.05$). Specific changes associated with LVAB were the development of Q-wave and ST-segment displacement (Table 2), but each ECG finding was noted in < 12% of patients.

Table 3 summarized the result of a multivariate analysis for factors associated with the development of LVAB. Among the clinical variables showing statistically significant difference between groups, sepsis was the only variable associated with the development of LVAB (odds ratio [OR], 9.2; 95% confidence interval [CI], 2.4 to 35.8; $p < 0.001$). The causes of sepsis were hepatobiliary sepsis (n = 7), pneumonia (n = 5), urosepsis (n = 4), wound infection (n = 3), febrile neutropenia association with chemotherapy (n = 3), meningitis (n = 1), peritonitis (n = 1), and deep neck infection (n = 1). Specific types of sepsis and microorganisms were not associated with the development of LVAB.

Of the 26 patients with LVAB, 21 (81%) presented with it on their first day in the ICU, whereas follow-up echocardiography showed its later development in the other 5 patients (19%), each of whom had normal echocardiogram findings at ICU admission. A myocardial perfusion scan using ^{201}Tl could be performed in 11 patients (42%), 10 of whom showed normal myocardial perfusion. During their

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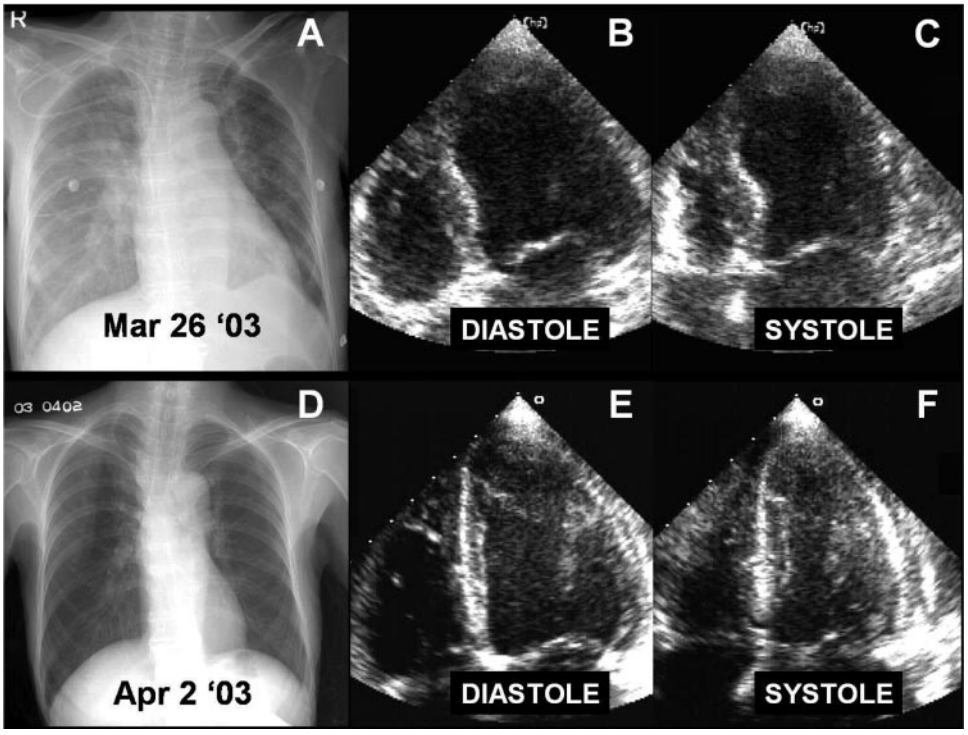

FIGURE 2. Representative chest radiograph and echocardiographic changes. This patient was a 65-year-old woman with cervical cancer and bilateral hydronephrosis. She was admitted to the hospital for high fever and oliguria, and a percutaneous nephrostomy and blood culture revealed urosepsis due to *Pseudomonas aeruginosa*. She complained of severe dyspnea, and a marked opacification of both lung fields was observed on a chest radiograph taken on the night of hospital admission (*top left*, *A*). ECG changes were nonspecific, but echocardiography showed the development of typical LVAB (*top middle*, *B*, and *top right*, *C*). Her condition was successfully managed, and she survived, with follow-up echocardiography showing the complete normalization of the wall motion abnormality and ejection fraction (*bottom middle*, *E*, and *bottom right*, *F*), and with disappearance of cardiomegaly and pulmonary edema (*bottom left*, *D*).

hospital stay, a normalization of LVAB and left ventricular ejection fraction with clinical improvement was documented in 20 of 26 patients (77%) a mean duration of 7.4 ± 5.6 days later (range, 2 to 25 days). Thirty of 92 patients (33%) died during management in the ICU. Among them, 12 patients showed typical LVAB, and the causes of death were sepsis in 9 patients and respiratory failure in 3 patients. No patients underwent autopsy. The mean 2-month survival rate was significantly lower in patients with LVAB (71 ± 6% vs 52 ± 12%, respectively; $p = 0.049$). Hypotension (*ie*, systolic BP, < 90 mm Hg) and APACHE III score on ICU admission were independent factors associated with mortality (Table 4).

DISCUSSION

Stress-Induced Cardiomyopathy in Critically Ill Patients

Japanese investigators have found that both emotional or mental stress, as well as physical stress, contributes to the development of LVAB, with death or funeral of a family member, quarreling, and vigorous excitation being common preceding events.[3,5] Several cases, however, were associated with underlying medical disorders, including exacerbation of bronchial asthma and noncardiac medical procedures including surgery. We have shown here that LVAB seems to be relatively frequent in critically ill patients who are admitted to medical ICUs due to noncardiac diseases.

The previous studies focused on the differentiation of this syndrome from classic acute myocardial infarction, thus using very strict diagnostic criteria, which included invasive coronary angiography to rule out "myocardial stunning."[1–3] This clinical syndrome has been established and can be easily diagnosed by bedside echocardiography, thus enabling the simplification of diagnostic criteria in some clinical situations. The differential diagnosis of wall motion abnormalities due to anterior wall myocardial infarction is not so difficult, because, in patients with LVAB, akinesia develops almost symmetrically, saving only

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Table 1—*Baseline Clinical Characteristics

Characteristics	Apical Ballooning − (n = 66)	Apical Ballooning + (n = 26)	p Value
Age, yr	63.3 ± 12	63.3 ± 10	0.968
Male sex	48 (73)	17 (65)	0.612
Risk factor for atherosclerosis			
Hypertension	24 (36)	4 (15)	0.077
Smoking	29 (44)	13 (50)	0.647
Diabetes	17 (26)	9 (35)	0.445
Reason for intensive care			
Hypoxia/hypercarbic respiratory failure	36 (55)	10 (39)	0.247
Sepsis	9 (14)	16 (61)	< 0.001
Comatose mentality	6 (9)	0 (0)	
Hemoptysis/hematemesis	6/5	0/0	
APACHE score	68.8 ± 33.4	83.6 ± 33.8	0.062
Hypotension on hospital admission	22 (33)	18 (69)	< 0.001
Volume resuscitation	20 (30)	16 (62)	0.009
Use of inotropic agents	21 (32)	18 (69)	0.002
Ventilator support	42 (66)	18 (69)	0.809
Hospital stay, d	34.2 ± 30.2	25.7 ± 17.9	0.185
2-month survival rate, %	71 ± 6	52 ± 10	0.047

*Values given as mean ± SD or No. (%), unless otherwise indicated. + = with apical ballooning; − = without apical ballooning.

the basal part of the left ventricle. In contrast, this rarely happens during myocardial infarction in patients without a history of multiple previous episodes of myocardial infarction.[2]

The detection of LVAB seems to have a tremendous prognostic impact, especially in critically ill patients. In previous studies, including case reports, the prognosis of LVAB was reported to be excellent, with only 1 of 88 patients (1.1%) dying after recurrence. Thus, the transient nature of this syndrome has been considered to be one of its characteristic features.[3] In our study, however, the development of LVAB was associated with a lower survival rate, which was likely due to differences in patient populations. Since enhanced or increased myocardial performance is anticipated to compensate for the increased systemic oxygen uptake in critically ill patients,[8] the poorer clinical prognosis seen in patients who developed LVAB with reduced left ventricular ejection fraction was expected. The finding that hypotension (*ie*, systolic BP, < 90 mm Hg) on ICU admission and APACHE III score were independent factors associated with mortality in this study represents the fact that the hemodynamic impact of LVAB is variable among patients and suggests the impor-

Table 2—*Comparison of Laboratory Findings

Variables	Apical Ballooning − (n = 66)	Apical Ballooning + (n = 26)	p Value
Catecholamine level (log value)			
Epinephrine	2.2 ± 0.7	2.4 ± 0.7	0.336
Norepinephrine	2.5 ± 0.7	3.2 ± 1.0	0.004
C-reactive protein, mg/dL	11.0 ± 10.3	17.2 ± 13.5	0.023
Cardiac enzymes			
Creatine kinase, U/L	177.1 ± 638.9	452.3 ± 672.3	0.119
Creatine kinase-MB, ng/mL	2.8 ± 3.4	7.9 ± 9.5	0.026
Troponin-I, ng/mL	0.4 ± 0.5	1.2 ± 1.6	0.047
ECG	12 (18)	16 (62)	< 0.001
T-wave changes	12	8	0.261
Q wave	0	3	0.021
ST-segment elevation	0	3	0.001
ST-segment depression	0	2	0.001

*Values given as mean ± SD or No. (%), unless otherwise indicated.

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Table 3—*Multivariate Analysis for Factors Associated With Development of LVAB*

Variables	OR	95% CI	p Value
Sepsis	9.20	2.36–35.79	< 0.001
Hypotension on hospital admission	1.54	0.33–7.16	0.585
Volume resuscitation	1.73	0.43–6.96	0.438
Use of inotropic agents	0.72	0.14–3.85	0.704
APACHE score on hospital admission	1.01	0.99–1.02	0.507

tance of the individual evaluation of cardiac status in this selected group of patients.

The mechanism of LVAB still remains elusive. In our study, sepsis and hypoxemia with respiratory failure were underlying diseases that were associated with the development of this syndrome. Marked alterations of arterial carbon dioxide and oxygen tension are not thought to cause left ventricular dysfunction, although moderate hypoxia can reduce the coronary flow reserve.[9] In this study, there was no statistical difference in the frequency of respiratory failure and ventilator support between patients who developed LVAB and those who did not. Interestingly, we found that sepsis patients were 54 times as likely to have a myocardial dysfunction as nonsepsis patients (95% CI, 1.7 to 1737.1; p = 0.024), and LVAB was detected in 64% of patients with sepsis. Extensive investigations have focused on left ventricular performance in patients with sepsis. Reversible left ventricular dysfunction has been well-documented in some patients with sepsis, and circulating factors, including lipopolysaccharides, cytokines, and prostanoids, and local factors, such as nitric oxide, have been suggested as potential etiologic mechanisms of "septic myocardial depression."[10–12] It is interesting to note that left ventricular dysfunction in sepsis has been described as a "global phenomenon" based on hemodynamic parameters including cardiac index.[13,14]

The development of segmental wall motion abnormalities has been shown to be a classic feature of septic shock, in that, using serial radionuclide assessment of left ventricular performance, 63% of patients (22 of 35 patients) with culture-proven septic shock had segmental wall motion abnormalities, whereas only 11% (4 of 35 patients) had generalized wall motion abnormalities.[15] Hemodynamic parameters, however, were of no value in predicting the development of left ventricular dysfunction in these patients.[15,16] Although reversible segmental left ventricular dysfunction has been considered a hallmark of "stunned myocardium" due to prolonged myocardial ischemia associated with epicardial coronary artery disease,[17] this phenomenon can occur without significant myocardial ischemia, and it can be increasingly diagnosed, especially by cardiac imaging, including echocardiography.[2,18]

The only common element of sepsis and respiratory failure in our patients would be stress-induced intense activation of the sympathetic nervous system. Catecholamines can directly injure the myocardium,[19–23] but this injury could be blocked by pharmacologic sympathetic blockade.[24] Some patients with typical LVAB showed persistent defects on ^{123}I-metaiodobenzyl-guanidine scans,[3] and an autopsy of a patient with sepsis and typical LVAB showed contraction band necrosis of the myocardium, which is a characteristic finding of catecholamine toxicity in patients with shock syndrome.[18,25] Although these results may have an important association with our finding that norepinephrine levels were higher in patients with LVAB, it may be the result, rather than the cause, of the development of LVAB. Moreover, it is also unclear why the injury is segmental, saving the basal part of the left ventricle. The possibility of regional differences in either sympathetic innervation or catecholamine receptor density should be further investigated[2] with the evaluation of levels of circulating factors such as natriuretic peptide, lipopolysaccharides, prostanoids, and cytokines in order to better define this transient ventricular dysfunction.

Table 4—*Multivariate Analysis for Factors Associated With Mortality*

Variables	OR	95% CI	p Value
Sepsis	0.89	2.36–35.79	0.874
Hypotension on hospital admission	9.34	1.62–53.73	0.012
APACHE score on hospital admission	1.02	1.00–1.04	0.031
Development of LVAB	1.76	0.48–6.46	0.392
Volume resuscitation	0.21	0.04–1.01	0.052
Use of inotropic agents	0.84	0.16–4.42	0.704

Limitations

Invasive coronary angiography was not performed to rule out the possibility of epicardial coronary artery disease. Patient care in the medical ICU, where > 65% of the patients received mechanical ventilatory support, did not allow for not only invasive angiography but also for a noninvasive myocardial perfusion scan, which needs stress testing for the complete evaluation of coronary flow reserve. Although segmental dysfunction can occur more frequently in patients with ischemic heart disease, we excluded any patients with any previous cardiac disease. The profile of risk factors for atherosclerosis was therefore similar in patients with and without

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LVAB. Moreover, echocardiography can easily differentiate between typical left LVAB and anterior wall myocardial infarction due to the symmetric involvement of the left ventricular wall saving the basal part in LVAB, which is beyond the territory of the left anterior descending artery.[2] Thus, it is unlikely that the low possibility of occult ischemic heart disease can change the main findings of this study. The low frequency (9%; 1 of 11 patients) of abnormal perfusion in thallium scans among our patients with LVAB also supports our contention.

The incidence of LVAB in our study needs careful interpretation. Since we selected patients with an acceptable window for transthoracic echocardiography, the real incidence of this abnormality would be different using other imaging modalities, such as transesophageal echocardiography, for patients with poor windows. In addition, we excluded patients who had been admitted to the surgical ICU for critical care immediately after surgical procedures. Surgery, however, would be expected to be another powerful triggering event for LVAB, making further study necessary.

Conclusions

Among patients receiving critical care in the medical ICU, LVAB with left ventricular dysfunction is a not infrequent occurrence, and echocardiography appears to be useful in diagnosing this phenomenon. Since the sensitivity for specific ECG changes was low, and elevated cardiac enzyme levels were detected in $< 50\%$ of patients with LVAB, routine echocardiographic screening and follow-up seems to be the only effective method for detecting this potentially fatal event, especially in patients with sepsis. Hand-held miniature echocardiography can thus be a useful tool, which is expected to be more frequently used in the near future.[26,27]

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