ABSTRACT. Background. The pathogenesis of acute pulmonary edema and cardiac collapse after enterovirus 71 (EV71) infection are not completely understood.

Objective. To determine the hemodynamic features and the mechanism of pulmonary edema (PE) after EV71 infection by direct intracardiac monitoring.

Design. Prospective clinical and laboratory study at a tertiary medical center.

Participants. Five consecutive infants, ages 2 to 13 months, with EV71 infection—proved by viral isolation in 4 and antibody in 1—with PE were enrolled. The clinical characteristics were systematically assessed. Hemodynamic profiles were determined every 4 hours by simultaneously implanted pulmonary arterial and central venous catheters during the acute stage.

Results. Magnetic resonance imaging revealed that all 5 infants had brainstem lesions. All patients had tachycardia and hyperthermia. Transient systolic hypertension was noted in 1 patient, and 1 presented with hypotension. Pulmonary artery pressure in all 5 infants was normal or mildly elevated (26–31 mm Hg), and central venous pressure ranged from 10 to 22 mm Hg. Pulmonary artery occlusion pressures were normal or slightly elevated (13–16 mm Hg). Systemic and pulmonary vascular resistances were transiently increased in only 1 patient. The stroke volume index decreased to 15.3 to 35.7 mL/M² (normal: 30–60 mL/M²), but because of the elevated heart rate, the cardiac index did not decrease. All hemodynamics normalized within days.

Conclusion. Fulminant EV71 infection may lead to severe neurologic complications and acute PE. The acute PE and cardiopulmonary decompensation in EV71 infection are not directly caused by viral myocarditis. The mechanism of PE may be related to increased pulmonary vascular permeability caused by brainstem lesions and/or systemic inflammatory response instead of increased pulmonary capillary hydrostatic pressure. Pediatrics 2002;109(2). URL: http://www.pediatrics.org/cgi/content/full/109/2/e26; enterovirus 71, pulmonary edema, pathogenesis, hemodynamics, hand-foot-mouth disease.

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ABBREVIATIONS. EV71, enterovirus 71; PE, pulmonary edema; PH, pulmonary hemorrhage; CNS, central nervous system; CK, creatine kinase; PAP, pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; MRI, magnetic resonance imaging.

Enterovirus 71 (EV71) has caused acute fatal epidemics in at least 5 regions of the world, including Malaysia and Taiwan. In 1998, an epidemic of EV71 infection affected >90 000 children in Taiwan. Among the 405 children hospitalized with acute neurologic disease, 78 died. In this outbreak, there was clinical, neuroradiologic, and pathologic evidence that the chief neurologic complication was rhombencephalitis or brainstem lesions. Most of the fatal cases initially involved minor neurologic symptoms, but the children rapidly died of acute onset of pulmonary edema (PE) and/or hemorrhage (PH) with rapid progression of cardiopulmonary failure within hours after admission.

The pathogenesis of acute fatality with PE alone or PE and concurrent PH during EV71 infection is not completely understood. Although several mechanisms, including central nervous system dysfunction and myocarditis, have been proposed, the alternation of cardiopulmonary function and its direct relationship to mortality have never been clarified. In this study, we continuously monitored the hemodynamic changes of this unusual, nearly fatal disease in 5 patients during the acute stage.

PATIENTS AND METHODS

From May to July 2001, 5 consecutive infants who had EV71 infection with central nervous system (CNS) involvement and PE and who required mechanical ventilation were enrolled. Three of the 5 also had PH. EV71 infection was defined as acute illness plus the isolation and typing of EV71 from rectal swab, throat swab, or cerebrospinal fluid, or increasing viral antibody titers determined by neutralization assay, as reported previously. CNS involvement was defined as pleocytosis in cerebrospinal fluid and symptoms of encephalitis or rhombencephalitis such as myoclonic jerks, oculomotor paresis, or bulbar palsy. PE was defined as alveolar congestion on chest radiography, and PH as fresh blood or pink, frothy fluid from the endotracheal tube.

Data were collected for age, sex, body weight, and clinical symptoms and signs on admission and during the entire course of disease. Laboratory investigations of plasma included a complete blood count, C-reactive protein, blood sugar, aspartate aminotransferase, alanine aminotransferase, total lactate dehydrogenase, electrolytes, creatine kinase (CK), and CK-MB isoenzyme. Cerebrospinal fluid analysis was performed for cell count, sugar, and protein. Virology studies included viral isolation from the throat and rectum, and paired serologic tests for EV71.

A 5-F pulmonary artery catheter was inserted soon after the infant was placed on mechanical ventilation. A full set of hemodynamic measurements was performed, including heart rate, arterial pressure, central venous pressure, pulmonary artery pressure (PAP), pulmonary artery occlusion pressure (PAOP), and cardiac output. From these measurements, and corrected for height and weight, the following derived variables were calculated: cardiac index (CI), systemic vascular resistance index, pulmonary vascular resistance index, left ventricular stroke work indices (LVSWI), and right ventricular stroke work indices. Central body temperature was also recorded by pulmonary artery
catheter thermosensor. All hemodynamic measurements were repeated 3 times and the mean value recorded. The hemodynamic profiles were conducted every 4 hours until the hemodynamics became stable. In addition to intravenous immunoglobulin, intravenous inotropic agents of dobutamine (4–16 μg/kg/min) and milrinone (0.25–0.4 μg/kg/min) were used based on hemodynamic changes. Dopamine (4–16 μg/kg/min) was added if hypotension occurred.

All patients received brain magnetic resonance imaging (MRI) within 5 to 9 days after admission.

RESULTS

The 5 infants were males whose ages ranged from 2 to 13 months. Three of them had hand-foot-mouth disease, and 2 had herpangina. Three patients had suffered from myoclonic jerks and the other 2 had oculomotor paresis before onset of PE. All chest radiographs were initially normal and then, after the onset of PE, showed diffuse alveolar density without obvious cardiomegaly (Fig 1). All patients had the frothy secretion characteristic of PE, and 3 had evidence of PH, fresh blood from the endotracheal tube after intubation. Arterial blood gases showed hypoxemia and metabolic acidosis in all cases. All had peripheral blood leukocytosis with left shifting and platelet counts greater than 300 000/μL. Disseminated intravascular coagulation profiles (prothrombin time, partial thrombin time, fibrinogen, and fibrinogen degradation products) were within normal ranges, except for patient 2, who had prolonged prothrombin time (1.4 × normal) and partial thrombin time (1.9 × normal). The CK-MB/CK ratios ranged from 1.1% to 5.8% (mean: 3.7%). Cerebrospinal fluid examination showed pleocytosis, normal sugar level, and increased protein concentration. All patients showed variable degrees of bright signal changes in T2 images of the brainstem on MRI. The clinical manifestations, laboratory studies, and radiologic findings are summarized in Table 1.

Initial hemodynamic measurements are summarized in Table 2. Tachycardia was the most common finding. Therefore, although stroke volume index was below normal values (30–60 mL/M²) in 4 cases, the CI was not decreased because of the elevated heart beat. High fever was another common finding: 2 patients had central hyperthermia up to 41.5°C. PAP was normal or mildly elevated (26–31 mm Hg in systole) and <40% of systemic pressure in all patients. Central venous pressure ranged from 10 to 22 mm Hg. PAOP was normal or slightly elevated (13–16 mm Hg). During admission, only 1 patient (patient 4) had transient systolic hypertension (up to 140/66 mm Hg) and transient increase of both systemic and pulmonary vascular resistance. Another (patient 2) had transient hypotension (65/34 mm Hg) and decreased systemic vascular resistance, whereas the other 3 patients had normal blood pressure and vascular resistance. The CI was maintained in normal range throughout the study (range: 3.1–6.9 L/min/M²). All cardiac hemodynamic profiles became stable within 48 hours after admission when PE resolved (Fig 2).

The 2 patients (patients 3 and 4) who presented with mild PE without hemorrhage and with minimal brainstem lesions recovered with minimal neurologic sequelae. The other 3 patients, who presented with PE, PH, and extensive brainstem lesions, remained respirator-dependent and physically inactive most likely because of the lesions.

DISCUSSION

The most important findings of the present study are that 1) EV71 infection can lead to severe neurologic complications and acute PE with or without hemorrhage; 2) all patients with EV71 infection and PE had brainstem lesions; 3) viral myocarditis is not the direct cause of acute PE and cardiopulmonary failure in EV71 infection; and 4) the excessive central sympathetic activation resulting in vasoconstriction was not the major cause of PE or hemorrhage.

A strong etiologic link between EV71 and the histologic changes in the CNS is well-established.¹⁻⁶ However, the pathogenesis of PE in EV71 is still unknown. The autopsy findings and brain MRI stud-
TABLE 1. Clinical Manifestations, Laboratory Studies, Radiology Findings, and Outcome of EV71 Infection With PE

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age</th>
<th>Clinical Features</th>
<th>CSF Findings</th>
<th>MRI Findings</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(WBC/Pro/Glu)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M/8</td>
<td>HFMD, fever for 4 d; myoclonic jerk for 2 d, poor after 3 h</td>
<td>120/76/71</td>
<td>Thrust CTR:0.5</td>
<td>Recovery</td>
</tr>
<tr>
<td>2</td>
<td>M/5</td>
<td>Herpangina, fever for 3 d; myoclonic jerk at posterior pons</td>
<td>33/84/92</td>
<td>Sool PE CTR:0.5</td>
<td>Recovery</td>
</tr>
<tr>
<td>3</td>
<td>M/13</td>
<td>HFMD, fever for 6 d; myoclonic twitching, consciousness change</td>
<td>128/51/73</td>
<td>Throat PE CTR:0.5</td>
<td>Minor sequelae</td>
</tr>
<tr>
<td>4</td>
<td>M/11</td>
<td>HFMD, fever for 6 d; myoclonic twitching, consciousness change</td>
<td>26/35/64</td>
<td>Antibody titer increase CTR:0.47</td>
<td>Minor sequelae</td>
</tr>
<tr>
<td>5</td>
<td>M/2</td>
<td>HFMD, fever for 6 d; myoclonic twitching, consciousness change</td>
<td>294/98/102</td>
<td>Stool PE CTR:0.46</td>
<td>Minor sequelae</td>
</tr>
</tbody>
</table>

HFMD indicates hand-foot-mouth-disease; CSF, cerebrospinal fluid; WBC, white blood cell count (/mm$^3$); Pro, protein (mg/dL), Glu, glucose (mg/dL); CXR, chest radiograph; CTR, cardiothoracic ratio.

Nonetheless, the CI was normal in all patients. The decreased stroke volume index could be explained by the associated tachycardia. Nonetheless, the CI was normal in all patients.

Persistent high fever and tachycardia were the most common findings in these patients. Usually, when the fever subsided, the heart rate slowed down, which also suggested that the tachycardia might have been cause by hyperthermia and not from increasing sympathetic activities resulted from compensatory response to heart failure.

The reticular formation of the medulla, a vasomotor center, when damaged can result in autonomic nervous dysfunction and rapid cardiovascular collapse. In previous reports, patients with bulbar poliomyelitis also had an acute onset of PE and similar brain autopsy findings. Therefore, we believe it is reasonable to deduce that the reticular formation may be responsible for the occurrence of PE and acute cardiac collapse. Severity of damage to this area is also closely associated with clinical outcome in these patients.

Regarding the mechanisms of neurogenic PE, previous studies have emphasized the role of massive central sympathetic neural discharge. This massive discharge leads to peripheral vasoconstriction and displacement of blood from the periphery to the heart and pulmonary vascular bed. Consequently, the patient will have increased pulmonary capillary pressure and edema formation. In one animal study, PE could develop rapidly after massive central sympathetic activation, but the pulmonary vascular pressure had to increase to very high levels before severe PE developed. When arterial vasoconstriction develops, it may result in hypertension and secondary cardiac dysfunction. Some patients with severe EV71 infection had transient hypertension before acute onset of PE and decreased left ventricular ejection fraction by echocardiogram. However, we found that by direct cardiac monitoring, all 5 patients—who had acute PE—had normal or very mildly elevated PAOP and PAP. Only 1 patient (patient 4) had a transient increase of pulmonary vascular resistance index and systemic vascular resistance index. This may suggest that the development of acute PE may not be fully explained by the sympathetic storm after the brainstem injury. In this study, intravenous dobutamine was immediately given routinely when the patient had PE. Although the vasodilating effect of dobutamine may somewhat influence vascular resistance, the interference may be minimal because of the short delay before Swan-Ganz catheter insertion. Milrinone and dopamine were prescribed later based on the intracardiac he-
modynamic changes, so they should have had no
direct effect on the initial cardiac hemodynamics.
Pulmonary edema can develop because of increas-
ing hydrostatic pressure or alveolar-capillary mem-
brane permeability of the lungs. Evidence indi-
cates that the CNS lesion also could alter the pulmo-
nary vascular permeability and result in PE.17–20
Severe systemic infection could induce the release
of various cytokines, which may cause lung injury
that increases pulmonary permeability.21 All our pa-
tients had high fever, tachycardia, tachypnea, and
leukocytosis with left shifting, compatible with the
features of systemic inflammatory response syn-
drome.22 Based on our observations, the pathogene-
sis of PE after fulminant EV71 infection may be re-
lated to increased pulmonary vascular permeability
instead of increased pulmonary capillary hydrostatic
pressure.
The management of PE and PH in patients with
EV71 is important but difficult. Based on the hemo-
dynamic profile found in this study, we have the
following suggestions: 1) Because PE in EV71 infec-
tion is not resulting from excessive vasoconstriction
alone, vasodilators should be used with caution; 2)
cardiopulmonary function usually returns to nearly
normal within days, but the neurologic sequelae are
severe and usually permanent. Therefore, the use of
extracorporeal membrane oxygenation support or a
left heart assist device should be weighed carefully;
and 3) direct intracardiac hemodynamic monitoring

<table>
<thead>
<tr>
<th>TABLE 2. Initial Hemodynamic Measurement in Patients With EV71</th>
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<tbody>
<tr>
<td><strong>Patient 1</strong></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>CT °C</td>
</tr>
<tr>
<td>HR bpm</td>
</tr>
<tr>
<td>BP (S/D/M) mm Hg</td>
</tr>
<tr>
<td>PAP (S/D/M) mm Hg</td>
</tr>
<tr>
<td>CVP mm Hg</td>
</tr>
<tr>
<td>PAOP mm Hg</td>
</tr>
<tr>
<td>CI L/min/m²</td>
</tr>
<tr>
<td>SI mL/m²</td>
</tr>
<tr>
<td>SVRI dyne/s/cm²/m²</td>
</tr>
<tr>
<td>PVRI dyne/s/cm²/m²</td>
</tr>
<tr>
<td>LVSWI gm/m²</td>
</tr>
<tr>
<td>RVSWI gm/m²</td>
</tr>
</tbody>
</table>

CT indicates core temperature; HR, heart rate; BP, blood pressure; S/D/M, systolic/diastolic/mean; CVP, central venous pressure; SI, stroke index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; LVSWI, left ventricular stroke work index; RVSWI, right ventricular stroke work index.

Fig 2. A, Sequential changes over 48 hours of PAOP; B, CI; C, pulmonary vascular resistance, and D, systemic vascular resistance.
may provide additional information to guide critical care.

CONCLUSION

Acute PE may be related closely to increased pulmonary vascular permeability caused by brainstem lesions and/or severe viral infection. Acute cardiopulmonary decompensation in patients with fulminating EV71 infection, however, is not caused by myocarditis itself but most probably by the damage to the vasomotor center of the brainstem. The excessive central sympathetic activation resulting in vasoconstriction was not the major cause of PE or PH.

ACKNOWLEDGMENT

We thank Professor Mei-Hwan Wu (Department of Pediatrics, National Taiwan University Hospital) for reviewing this manuscript.

REFERENCES

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Pediatrics 2002;109;e26
DOI: 10.1542/peds.109.2.e26

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