The factors underlying the hyperdynamic circulation in cirrhotic portal hypertension are incompletely understood. Hepatic dysfunction and portal-systemic collaterals may allow certain vasodilator substances (glucagon, prostaglandins, nitric oxide) to escape hepatic inactivation leading to local or systemic vasodilatation. 3,5,14 A reduced vascular sensitivity to endogenous vasoconstrictors may also contribute.14 The opening of preformed but functionally inactive arteriovenous anastomoses by a vasodilator substance was postulated over 30 years ago by Murray et al.2 In fact, arteriovenous malformations in the skin, splanchnic vascular bed, and pulmonary circulation are known sequelae of cirrhosis.2,4 Sodium retention accompanies systemic vasodilatation and may contribute to the hyperkinetic circulation in cirrhosis.5,5

The hepatopulmonary syndrome describes the clinical relationship between chronic liver disease and intrapulmonary vascular dilatations that result in abnormal pulmonary gas exchange and an increased alveolar-arterial oxygen gradient.15,16 Clinical manifestations include dyspnea, digital clubbing, platypnea, and orthodeoxia.15,16 The hyperdynamic circulatory state of liver disease may accompany the hepatopulmonary syndrome and influence the level of arterial hypoxemia present.16 As with high-output state in portal cirrhosis, the cause of the abnormal pulmonary vascular physiology in this condition remains unclear.

The worsening hyperdynamic state after surgical portal-systemic anastomosis and TIPS is poorly understood and of uncertain long-term importance. These procedures reduce hepatic blood flow and may exacerbate encephalopathy from failure to metabolize offending substances. Likewise, the increased cardiac output after shunting may result from the failure to clear a putative vasodilator substance.

The patient described in our report developed clinically significant high-output congestive heart failure after TIPS and returned to baseline immediately after liver transplantation. While the hyperkinetic circulation of cirrhosis has rarely been reported to be associated with congestive heart failure,5 our report documents that some patients without underlying cardiac disease may develop this syndrome after TIPS.

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Acute, Reversible Left Ventricular Dysfunction in Status Asthmaticus*

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Three cases of rapidly reversible severe myocardial depression are described in patients with status asthmaticus. Initial echocardiograms obtained within 1 day of hospital admission revealed global left ventricular hypokinesis with ejection fractions of 11 to 34%. Follow-up echocardiograms obtained only 3 to 8 days later revealed marked improvement of left ventricular function. Possible mechanisms responsible for the observed rapidly reversible myocardial depression and the clinical implications of this finding are discussed.

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Key words: asthma; left ventricular dysfunction; myocardial depression; respiratory failure

Although most cases of asthma are easily treated in the outpatient setting, emergency department, or general medical floor, asthma exacerbations can also become life threatening. In fact, several thousand people die of asthma each year.\(^1\,^2\). The cause of death in these individuals has not been clearly defined, but hypoxemia and cardiac death secondary to medications such as \(\beta\)-agonists have been implicated as one possible mechanisms for the asthma deaths. It is thus important to treat not only the direct causes of severe asthma attacks, but also to recognize and treat any contributory factors to the patient's compromised respiratory status. We report three cases of severe, reversible left ventricular dysfunction occurring in the setting of status asthmaticus that contributed to patients' compromised respiratory status.

CASE REPORTS

CASE 1

A 45-year-old woman with a history of steroid-dependent asthma since age 25 years was brought to the emergency department in respiratory distress after several weeks of upper respiratory tract infection symptoms and worsening asthma. The patient had never smoked, had no other medical history, and had been hospitalized twice previously for asthma exacerbations, but never intubated. Her current medical regimen included prednisone, 10 mg orally every day, theophylline, and \(\beta\)-agonist inhalers. A blood gas sample drawn in the emergency department revealed a \(\mathrm{PaO}_2\) of 32 mmHg, which may have been a venous blood gas, given a documented oxygen saturation of 100% on nonrebreather face mask around the time this blood gas was drawn. Despite aggressive medical treatment in the emergency department, the patient remained markedly tachypneic and in respiratory distress and she was therefore intubated. Chest radiograph showed mildly hyperinflated lung fields but no pulmonary vascular congestion, effusions, or cardiomegaly. Over the next 24 h, the patient remained difficult to ventilate with a peak inspiratory pressure on the ventilator of 60 cm \(\mathrm{H}_2\mathrm{O}\) and an auto-PEEP of 18 cm \(\mathrm{H}_2\mathrm{O}\), \(\mathrm{Paco}_2\) levels 64 to 70 cm \(\mathrm{H}_2\mathrm{O}\), and arterial \(\mathrm{pH}\) ranging from 7.05 to 7.18. She was treated with albuterol nebulizers (2.5 mg every 90 min, total dose over the first 12 h of 25 mg), intravenously (IV) methylprednisolone, 125 mg every 6 h, and IV theophylline, 30 mg/h, as well as infusions of vecuronium bromide, midazolam, and sodium bicarbonate (Table 1). A repeated chest radiograph 6 h into therapy was remarkable for pulmonary edema (Fig 1). One day after hospital admission, the patient developed diffuse T-wave abnormalities on her ECG (Fig 2) and was noted to have a mildly elevated total creatine phosphokinase (CPK) level of 224 U/L (normal, 40 to 180 U/L) with a mildly elevated CPK-MB level of 10.1 ng/mL (normal <3 ng/mL). A cardiac echo was obtained that revealed global hypokinesis with apical akinesis. Left ventricular ejection fraction was calculated to be 31%. Right ventricular function was normal.

The patient was treated for both asthma exacerbation and congestive heart failure with the addition of intravenous furosemide. The frequency of \(\beta\)-agonists was reduced to every 4 to 6 h. Over the next several days, the patient's respiratory status improved and on hospital day 3, she was extubated. After extubation, the patient complained of several episodes of chest pain. Because of the chest pain, ECG abnormalities, CPK-MB elevation, depressed ejection fraction, and congestive heart failure, she underwent cardiac catheterization, that demonstrated completely normal epicardial arteries. Right ventricular biopsy was also performed and revealed no evidence of inflammation.

Table 1—Medications Administered to Each Patient During the First 12 h of Hospitalization

<table>
<thead>
<tr>
<th>Medications Administered</th>
<th>Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Albuterol (mg nebulized)</td>
<td>25</td>
</tr>
<tr>
<td>Sodium bicarbonate (mEq IV)</td>
<td>350</td>
</tr>
<tr>
<td>Vecuronium bromide (mg IV)</td>
<td>30</td>
</tr>
<tr>
<td>Aminophylline (mg IV)</td>
<td>360</td>
</tr>
<tr>
<td>Midazolam (mg IV)</td>
<td>40</td>
</tr>
<tr>
<td>Diazepam (mg IV)</td>
<td>0</td>
</tr>
<tr>
<td>Ipratropium bromide (puffs)</td>
<td>0</td>
</tr>
<tr>
<td>Methylprednisolone (mg IV)</td>
<td>375</td>
</tr>
<tr>
<td>Epinephrine (mg SQ)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Figure 1.** Anteroposterior projection chest radiographs of patient 1 immediately following intubation (left) and 6 h later (right) demonstrating the development of extensive bilateral perihilar interstitial infiltrates.
performed that revealed scant polymorphonuclear leukocytic infiltration, no myocyte necrosis, and no evidence of active myocarditis. While not a normal finding, this finding alone, along with the lack of any pathologic evidence of myocyte necrosis, is neither diagnostic nor suggestive of active myocarditis. The patient's condition continued to improve and a follow-up echocardiogram was obtained 8 days after the first study. It demonstrated complete recovery of left ventricular function with a calculated left ventricular ejection fraction of 62%.

CASE 2

A 42-year-old nurse with long-standing asthma without a history of prior intubation experienced a relapse of her asthma after having just finished a self-dosed prednisone taper for a previous exacerbation. Her symptoms worsened over the next week, despite an increase in the frequency of her aerosolized bronchodilators to every 2 h. On the day of hospital admission, she sought help by driving to a fire station where she collapsed. She was bag masked for 10 min until an ambulance arrived, when she was intubated. At the time, her heart rate was noted to be 40 and her initial blood pressure was 60 mm Hg. In the emergency department, she was noted to be markedly bronchospastic with peak inspiratory pressure in the 70-cm H2O range, and was treated with steroids, aminophylline, subcutaneous (SQ) terbutaline, and SQ epinephrine X2 (Table 1). Because of continued difficulties ventilating the patient, paralytic agents were administered. Arterial blood gas demonstrated a moderate acidemia with pH values of 7.25 and a PO2 of 359 mm Hg. No clear hypoxemic episode was documented. Chest radiograph showed perihilar infiltrates consistent with pulmonary edema. A Swan-Ganz catheter was inserted and demonstrated a mean pulmonary wedge pressure of 23 mm Hg. In the intensive care unit, the patient was treated with frequent albuterol nebulizers (a total of 17.5 mg over the first 12 h), intravenous aminophylline, corticosteroids, diazepam, vecuronium, and ipratropium bromide metered-dose inhalers (Table 1). Over the first hospital day, the patient's ECGs evolved inferolateral T-wave inversions and a chest radiograph demonstrated pulmonary edema. A cardiac echo was obtained, which showed severely depressed left ventricular function with global hypokinesis and apical dyskinesis and a calculated ejection fraction of 11%. Right ventricular function was normal. No elevation in CPK-MB level was detected.

With diuretic therapy and afterload reduction, the pulmonary wedge pressure gradually declined, although the patient continued to have episodic severe bronchospasm and remained intubated for several more days. A follow-up echo obtained 3 days after hospital admission while the patient was still intubated showed the left ventricular ejection fraction was now normal and was calculated to be 68%.

CASE 3

A 27-year-old woman with a history of asthma since childhood, two respiratory arrests at age 2 years, multiple previous intubations for asthma, multiple steroid tapers, smoking, and cocaine abuse was found unresponsive with agonal respirations at home by her children. She had had a sore throat and increased wheezing and shortness of breath for a week prior to this incident. The only medication she was taking was a β-agonist metered-dose inhaler. Initial emergency medical technician assessment revealed a pulse of 130 beats/min with a blood pressure of 210/100 mm Hg. She was administered naloxone hydrochloride (Narcan) and treated with two metoproterenol sulfate (Alupent) nebulizers. In the emergency department, the patient's examination was notable for diffuse prolonged expiratory wheezes. An initial blood gas obtained while the patient was intubated and being manually ventilated demonstrated a pH of 6.95, PCO2 of 71 mm Hg, and PO2 of 71 mm Hg on high-flow oxygen. Qualitative urine toxicology was positive for cocaine and negative for other toxins.

The patient remained difficult to ventilate while receiving mechanical ventilatory assistance respirator with peak inspiratory pressure in the 60 cm H2O range and an auto-PEEP of 15 cm H2O. A blood gas value on ventilator settings of intermittent mandatory ventilation=12, tidal volume=1,000 mL, and FIO2=100% revealed a PCO2 of 69 mm Hg and a pH of 7.05. The patient was subsequently paralyzed. Chest radiograph obtained in the emergency department showed a normal sized heart and clear lung fields.

The following day, the patient remained difficult to ventilate with PaCO2 levels in the range of 66 to 95 mm Hg and arterial pH in the range of 7.09 to 7.23. Her ECG demonstrated 0.5-mm ST segment elevation in leads I and aVL and modest T-wave inversions in the anterolateral leads. The first two CPK-MB levels were slightly elevated at 13.3 ng/mL and 17.4 ng/mL (normal <3 ng/mL). Repeated chest radiograph demonstrated new pulmonary edema. An echocardiogram was obtained and demonstrated global hypokinesis with a calculated ejection fraction of 34%.
Right ventricular function was normal.

The patient’s hospital course was complicated by Moraxella catarrhalis pneumonia. Five days after hospital admission, she was found to have one of six blood cultures positive for Staphylococcus aureus, that was believed to be secondary to a venous catheter and line-related bacteremia. The patient was extubated on hospital day 7. The ECGs at this time demonstrated normalization of the previous T-wave abnormalities with the ST elevations returning to baseline and no evolution of Q waves. A follow-up cardiac echo obtained 9 days after hospital admission and 8 days after the first echo now showed that the ejection fraction had improved to 50%.

**DISCUSSION**

We have been able to locate only one other reported case of rapidly reversible left ventricular dysfunction in the setting of asthma. That case involved a 20-year-old woman who was intubated for respiratory arrest and suffered subsequent barotrauma. The patient was treated with high-dose catecholamines. She developed pulmonary edema 24 h after hospital admission and had a wedge pressure of 33 mm Hg and an ejection fraction measured by gated radionuclide cardiac scan of 17%. Her condition required placement of an intra-aortic balloon pump. By day 5, with the balloon pump removed, her ejection fraction had improved to 33%, and an ejection fraction measured several weeks later had returned to normal at 66%.

None of our three patients had any significant cardiac history or symptoms to suggest any baseline cardiac dysfunction or coronary artery disease. Although patient 3 had recently taken cocaine and did have a slight rise in her CPK-MB level, the rise was minimal. Even if this rise was due to a small amount of myocardial injury due to coronary vasospasm, it would not explain the global and profound left ventricular depression noted on the first cardiac echo. It thus seems likely that the observed myocardial depression in all three patients was associated with the events related to subsequent respiratory failure after the onset of the episodes of asthma exacerbation.

Several possible causes can be hypothesized to have contributed to or caused the observed myocardial depression. Pronounced or prolonged myocardial ischemia is known to be able to cause “myocardial stunning” in which there is temporary dysfunction, usually on the order of several days, of the ventricular myocardium. This phenomenon is almost exclusively observed in patients with significant coronary artery disease. However, none of the three patients described were known or suspected of having any coronary artery disease. Further, one was only 27 years old and a second patient had catheterization revealing no epicardial coronary artery disease.

Both severe hypotension and profound hypoxemia could produce myocardial ischemia in the absence of significant epicardial coronary artery disease. Both patients 2 and 3 did have observed hypotension, and it is possible that these two factors may have contributed to the left ventricular dysfunction. Further, although there were no documented episodes of severe hypoxemia, given the patients’ clinical presentations, significant hypoxemia is likely to have been present at some time, and hypotension, acidemia, or both may also have been present. The contribution of such factors to the observed myocardial depression is unclear.

Sepsis and septic shock have also occasionally been associated with myocardial depression. In one series of 20 patients admitted to an ICU who developed septic shock, 10 patients were observed to have ejection fractions measured by radionuclide cineangiography of below 40%, with three of these patients having measured ejection fractions below 20%. However, only one of the three patients described in this report had positive blood cultures (patient 3), and in this case it was 5 days after hospital admission and in only one of six blood cultures obtained, with the blood culture drawn 2 days after the echo was performed and drawn from a central line. None of the patients had persistent fevers (or hypothermia) or hypotension to suggest sustained bacteremia or clinical sepsis. It thus seems unlikely that sepsis was the cause of the observed myocardial depression.

There have been two cases of reported profound reversible myocardial dysfunction occurring in the setting of anaphylaxis, with histamine discussed as a potential myocardial depressor. Raper and Fisher have noted that there are histamine receptors in both animal and human hearts and that stimulation of these receptors has experimentally been shown to lead to myocardial depression. However, whether histamine released during the anaphylaxis actually leads to the observed myocardial depression, and whether it may have played a role in these three patients, remains only speculative. Further, none of the patients had clinical features of anaphylaxis with their asthma exacerbations.

Acidemia is generally suspected of being able to cause myocardial depression. However, there is surprising little published recent literature on this topic. In his book on cardiac physiology, Katz notes that “the negative inotropic actions of acidosis have been recognized since the work of Gaskell in 1880.” He states that high hydrogen ion concentrations can inhibit calcium binding to troponin, and that this may be one mechanism by which acidosis can decrease myocardial contractility. The degree to which acidosis can depress ventricular function and the time course of recovery of myocardial function after a period of acidosis remain poorly defined.

At the time that the initial cardiac echos were obtained, two of the patients were only mildly acidic with arterial pH values of approximately 7.20 to 7.23. The arterial pH value in the third patient was between 7.30 and 7.40 at the time of the initial cardiac echo. Thus, the contribution of acidemia, if any, to the observed myocardial depression, also is unclear.

Although myocarditis can cause ventricular dysfunction, the rapid improvement in ventricular function observed is not characteristic of myocarditis. Furthermore, the endomyocardial biopsy findings in patient 1 failed to show evidence of myocarditis.

Catecholamines have also been implicated in myocardial depression and dysfunction. Elevated catecholamine levels seen in pheochromocytoma have been associated with myocardial dysfunction. Catecholamines have also been associated with the formation of myocardial contraction bands. In a rat model, the cardiac toxicity of catecholamines was dramatically potentiated by pretreat-
ment with corticosteroids. There have been 73 cases of pulmonary edema associated with β2-sympathomimetic treatment for premature labor. The pulmonary edema usually resolved within 24 hours after withdrawal of the tocolytic agent and institution of diuretic therapy. The 20-year-old woman in the prior case report discussed above received high-dose epinephrine bolus (30 mg over 2 h) and IV infusion (0.8 μg/kg/min), salbutamol infusion (up to 40 μg/min), and isoproterenol (Isoprenaline) infusion (up to 0.33 μg/kg/min), as well as IV aminophylline and nebulized salbutamol, and the authors of the case report speculated that these high-dose catecholamines caused the myocardial depression. Three elderly persons hospitalized for COPD exacerbation receiving β-agonist inhalers and theophylline, who were found to have severely depressed ventricular function, were found on endomyocardial biopsy specimen and autopsy to have findings consistent with catecholamine-induced myocardial damage. However, two of the three patients died, and in the third patient, cardiac function did not return to normal for 8 months.

All three of our patients described in this report had been taking both inhaled β-agonists and theophylline (Theo-Dur) (although patient 2's theophylline level was <2 μg/mL) and also received additional sympathomimetics during their short-term treatment (Table 1). However, they predominantly continued to receive these treatments through the time of the follow-up echos. Further, one would not expect quick recovery of ventricular dysfunction that was due to myocardial contraction band necrosis. Thus, while experimental data suggest a possible role for catecholamine-mediated myocardial toxic reaction, the causative role, if any, of catecholamines in the observed ventricular dysfunction in these three patients remains unclear.

It is also possible that the observed pulmonary edema was noncardiac in origin. Pulmonary edema may also develop as a result of changes in interstitial hydrostatic and colloid osmotic pressures. However, in the cases of these three patients, the echocardiographic findings of severely reduced left ventricular function, the documented high pulmonary capillary wedge pressure in patient 2, and rapid clinical responses to diuretic and afterload reduction therapy, occurring within the time frame of the observed rapid improvement in ventricular function, suggest that the observed pulmonary edema was likely the result of congestive heart failure.

**CONCLUSION**

Although the cause or causes of the reversible left ventricular dysfunction in these patients remain unclear, it is clear that such a phenomenon does occur, and that myocardial dysfunction can further compromise the respiratory status in patients with status asthmaticus. Left ventricular dysfunction should therefore be suspected in patients with status asthmaticus who do not respond to usual treatment modalities, who have physical examinations suggestive of myocardial dysfunction, who develop unexplained ECG changes, or who demonstrate any signs of evolving pulmonary edema on a radiograph. Echocardiography should be performed in such patients, as prompt recognition and treatment of left ventricular dysfunction could lead to improvement in such patients' hospital course.

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