Reversed Ventilation-Perfusion Mismatch Involving a Pediatric Patient in Congestive Heart Failure

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Over the past 13 yr, at least 11 specific etiologies of reversed ventilation-perfusion mismatch have been reported in the literature. In this article, a case of reversed ventilation-perfusion mismatch involving a patient in congestive heart failure receiving dobutamine and milrinone therapy is presented. A brief review of the topic of reversed ventilation-perfusion mismatch is presented.

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To date, reversed ventilation-perfusion mismatch has been reported in the literature associated with airway obstruction (*1*), pulmonary arterial hypertension (*2*), chronic obstructive lung disease (*2*), pneumonia (*2*), bronchopulmonary dysplasia (*3*), atelectasis associated with mechanical ventilation using positive end expiratory pressure (*4*), lung transplant (*5*), pleural effusion (*2*), metabolic alkalosis (*6*) and embolic arterial obstruction of the opposite lung (*7*). It has also been reported as a transient phenomenon in a patient with squamous cell carcinoma of the lung (*8*). The following are possible etiologies of ventilation-perfusion mismatched currently reported in the literature:

Airway obstruction.
Pulmonary arterial hypertension.
Chronic obstructive pulmonary disease.
Pneumonia.
Bronchopulmonary dysplasia.
Atelectasis associated with mechanical ventilation using PEEP.
Lung transplant.
Pleural effusion.
Metabolic alkalosis.
Embolic arterial obstruction in the contralateral lung.
Squamous cell Ca of lung (transient).

CASE REPORT

A 13-yr-old boy was first presented with a 2-wk history of nausea, vomiting and diarrhea. The patient was short of breath and on physical examination had a "gallop" rhythm. The chest radiographic examination showed cardiomegaly, vascular congestion and mild interstitial edema. The patient was given a diagnosis of acute myocarditis and was started on medications of dobutamine, digoxin, spironolactone and furosamide.

An EKG study showed right-axis deviation and flattened T-waves. An echocardiographic examination demonstrated poor global myocardial function and a pericardial effusion. Viral studies performed including Epstein-Barr, Coxsackie types A and B, Echo types 4, 9, 11 and 30 and a Monospot test, all of which were negative. The patient's test for the Lyme's antigen was also negative. The patient's medications were optimized by adding milrinone and captopril to his regimen.

About 1 mo later, during a stay in the intensive care unit, the patient developed a dysrhythmia and shortness of breath with minimal exertion. Pulsoximetry found him to have a pO_2 saturation of 85% while receiving 95% O_2 therapy. Because of the acute exacerbation of his shortness of breath and his risk for development of mural thrombus, he was heparinized, and a ventilation-perfusion lung scan (V/Q scan) was ordered to exclude pulmonary embolism (Fig. 1).

The ventilation-perfusion lung scan was performed using 3 mCi of ^{99m}Tc-MAA and an ^{81m}Kr generator that was calibrated to 5 mCi min at 9 a.m. that morning. Paired ventilation-perfusion images of the lungs were acquired in the posterior and bilateral posterior oblique views with the patient supine. Additional perfusion images were obtained in the anterior and bilateral lateral views. Krypton images were acquired for 300,000 counts using a 190 keV peak with a 15% symmetric window. The technetium images were obtained, before each Krypton image, for 300,000 counts using a 140 keV peak with a 20% symmetric window. The examination was correlated with a portable AP chest radiograph obtained within 1 hr of the ventilation-perfusion study (Fig. 2).

The V/Q scan showed symmetric, bilateral, predominantly central and regional ventilatory defects, which were superimposed on a matched regional defect due to cardiomegaly. The perfusion scan showed little else than the regional defect due to the heart. These findings were interpreted as a reversed ventilation perfusion mismatch and unlikely to represent embolic pulmonary disease.

The patient had an endocardial biopsy that showed interstitial fibrosis and focal areas of hypertrophied myocytes. These findings were considered consistent with an idiopathic, dilated cardiomyopathy. The patient was placed on the cardiac transplant list, but further cardiac decompensation necessitated placement of a left ventricular assist device while the patient awaited transplantation.

DISCUSSION

The physiologic importance of reversed ventilation-perfusion mismatch is that it represents the return of admixed, hypoxic blood to the systemic circulation. Normally, hypoxia elicits a hypoxic vasoconstrictive response that shunts blood away from regions of lung hypoxia (*8*). Although it has been reported in patients after stellate ganglionectomy or pharmacological sympathectomy, suggesting a generalized response mechanism, the consensus has been that this response is a local phenomenon. This has been supported experimentally by an animal model. Therefore, reversed ventilation-perfusion mismatch may be segmental or generalized depending on the pathologic process that elicits it (*8*). Some of the explanations for the suppression of the normal hypoxic vasoconstrictive response are more straightforward than others. Few of the proposed mechanisms have yet to be proven in controlled studies.

In pneumonia, there is consolidation of air space by pus and debris. The suppression of the hypoxic vasoconstrictive response is believed due to the local release of inflammatory mediators with vasodilatory properties, such as prostacyclin (*9*).

Acutely elevated pulmonary arterial pressure can force a

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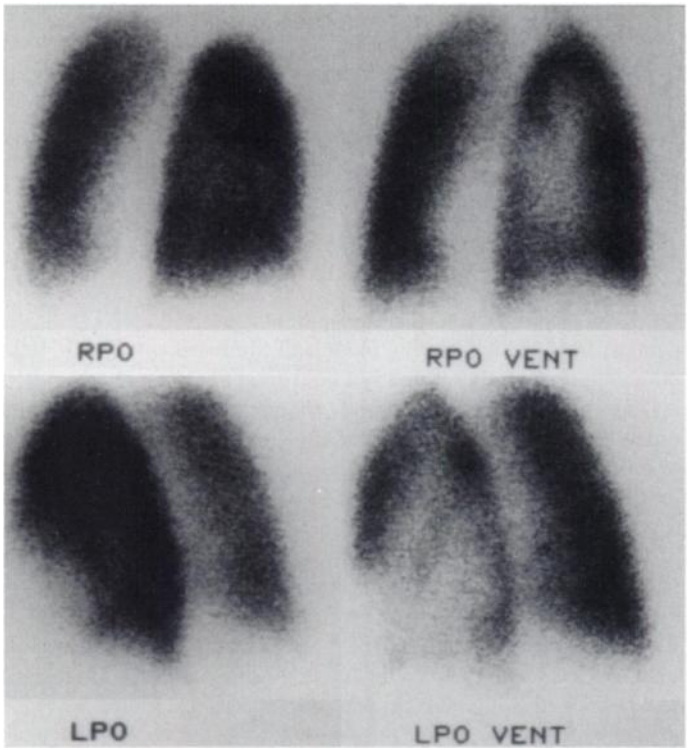

FIGURE 1. Excerpts from the ventilation-perfusion lung scan. Left to right: Perfusion and ventilation scans in the RPO projection (above) and LPO projection (below). Note the large symmetric central ventilation defects without matching abnormalities on the perfusion scans.

disproportionate amount of hypoxic blood through an otherwise normal contralateral lung in cases of massive unilateral pulmonary embolism (*7*). In primary pulmonary arterial hypertension, it has been hypothesized that there is either altered Laplace and Poiseuille forces, altered vascular response to hypoxia due to intimal hypertrophy and medial atrophy or a combination of these phenomena that cause a failure of the vasoconstrictive response (*2*). It seems likely that similar mechanisms drive the abnormal response to hypoxia in chronic obstructive lung disease, which ultimately leads to pulmonary arterial hypertension.

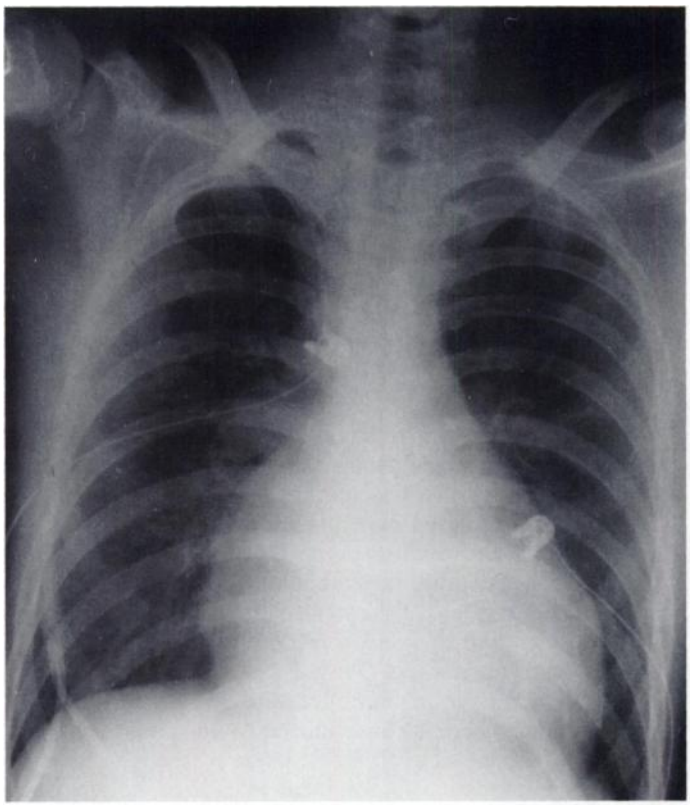

FIGURE 2. Posterior-anterior radiographic chest examination demonstrating cardiomegaly and vascular congestion.

Unilateral lung transplantation frequently results in an impaired hypoxic response of the transplanted lung. Although the exact mechanism is unclear, the disruption of normal innervation seems a likely cause (*8*). Characteristically, in bronchopulmonary dysplasia there is destruction of the peripheral capillary bed, but there may also be some disruption of normal innervation. However, in the one reported case there were confounding factors of atelectasis, and mechanical ventilation with positive end expiratory pressure which can lower the local pCO_2 and in so doing suppress the hypoxic response of vasoconstriction or cause local airway constriction that decreases local ventilation (*3*). The exact mechanism of the reversed ventilation-perfusion mismatch in this case could not be confidently determined.

Using an animal model, Enjeti et al. (*10*) explained reversed ventilation-perfusion mismatch in regions of lobar collapse during concomitant positive end expiratory pressure. They found that while total cardiac output through inflated lungs decreased, the shunt fraction doubled in the presence of lobar atelectasis. The same was not true for sublobar atelectasis. It seems likely that patients with large pleural effusions and bronchial obstruction develop reversed ventilation-perfusion mismatch by a similar mechanism.

The reversed ventilation-perfusion mismatch seen in a case report of squamous cell carcinoma of the lung was transient lasting 3 days. Blood gas and pulmonary arterial pressure were not monitored, and the author offered no explanation for the reversed ventilation-perfusion mismatch. Sostman et al. (*11*) discussed a case in which metabolic and respiratory alkalosis are believed to have suppressed normal hypoxic vasoconstriction.

In congestive heart failure, pulmonary edema can fill the alveoli and terminal bronchioles with fluid, which explains the ventilatory abnormality. It is the lack of the normal hypoxic vasoconstriction causing a reversed ventilation-perfusion mismatch that must be explained.

Although there is no intimal or medial response to acute congestive heart failure, there is elevation of pulmonary venous pressure leading to elevation of pulmonary arterial pressure. Thus, failure of hypoxic vasoconstriction can be explained by the mechanisms discussed by Engeler et al. (*2*) and Armas (*7*). Perhaps acute interstitial edema interferes with the ability of pulmonary arteries to constrict normally. The patient's hypoxia may have been periodically treated with supplemental oxygen, resulting in a failure of the local response to hypoxia much the same as the cases described by Slavin et al. (*3*).

From the late 1980s through the early 1990s, a series of articles appeared in the cardiology literature that introduced the concept of neurohumoral activation in patients with left ventricular dysfunction. These articles have focused on a half dozen or so neuropeptides that have both vasoconstrictive (i.e., arginine vasopressin and renin) and vasodilatory effects (i.e., atrial natriuretic peptide). It was found that in the postinfarction period, those patients who developed left ventricular dysfunction experienced a significant elevation of their blood levels of these neurohumoral substances. In general, 48% of patients with left ventricular dysfunction in the Survival and Ventricular Enlargement (SAVE) study had widespread activation of their neurohumoral axes, but there was a poor correlation between the levels of the individual neuropeptides versus the degree of

impairment of left ventricular ejection fraction. In all, 61% had a significant elevation of their atrial natriuretic peptide levels (*12*).

The exact mechanism by which elevated atrial natriuretic peptide levels are associated with a poor prognosis is uncertain because atrial natriuretic peptide promotes vasodilation, diuresis and suppresses activation of the renin-angiotensin system. These effects are typically associated with improvement rather than deterioration of the patient. However, Rouleau et al. (*13*) interpreted this paradox as atrial natriuretic peptide elevation representing a response to another, as yet undetermined, underlying pathologic process.

Finally, the patient was receiving dobutamine and milrinone therapy at the time of the ventilation-perfusion scan. Both drugs at low doses cause vasodilatation in addition to an inotropic effect on the heart.

Milrinone is a derivative of the bipyridine agent amrinone. These drugs are phosphodiesterase inhibitors that cause an increase of intramyocardial cyclic AMP concentration, presumably through enhanced calcium reuptake by the sarcoplasmic reticulum. In addition to the vasodilatory, and inotropic action of dobutamine, milrinone has the salutary effects of improved left ventricular diastolic function (lusitropic effect) and unlike dobutamine does not cause a significant increase of myocardial oxygen consumption (*14*). Eichhorn et al. (*15*) investigated the impact that milrinone has on the pulmonary circuit. They found that, unlike dobutamine, milrinone had a significant beneficial effect on the right ventricle. It reduced right ventricular afterload by decreasing pulmonary arterial wedge pressure. The latter is presumably due to significant pulmonary vasodilation. In addition, milrinone has an inotropic effect on the right ventricle not seen with dobutamine.

CONCLUSION

Perhaps atrial natriuretic peptide contributed to the suppression of the normal hypoxic vasoconstrictive response in our patient. Furthermore, it may be that the underlying pathologic process that portends a poor prognosis refered to by Rouleau et al. (*12*) is the admixture of shunted, hypoxic blood in the pulmonary vascular bed, thus causing acute oxygen desaturation as was seen in this case just before the ventilation-perfusion scan. The effect of milrinone on the pulmonary vasculature may block the normal vasoconstrictive response to hypoxia. Whether or not milrinone itself causes failure of the vasconstrictive response to hypoxia, in the presence of neurohumoral activation due to left ventricular dysfunction it seems to have done so in the patient of this case presentation.

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