The Clinical Physiologist

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Severe, Rapidly Reversible Hypoxemia in the Early Period after Bilateral Lung Transplantation

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In Brief

A recipient of a bilateral lung transplant developed moderate primary graft dysfunction after extubation on Postoperative Day 1. Early on the second postoperative day she became increasingly hypertensive, and a continuous infusion of nicardipine was started. After this she developed rapidly worsening, severe hypoxemic respiratory failure requiring supplemental oxygen administered via high-flow nasal cannula. Estimated $\text{PaO}_2/\text{FiO}_2$ dropped from 207 to 69. Hypoxemia responded quickly to an intervention that was based on an understanding of factors determining pulmonary gas exchange in this setting.

The Clinical Challenge

A 63-year-old woman with advanced lung disease from idiopathic pulmonary fibrosis underwent sternal-sparing, off-cardiopulmonary bypass, bilateral lung transplantation. An intraoperative transesophageal echocardiogram showed both pulmonary venous anastomoses as widely patent with appropriate flow velocity by Doppler. A perfusion scan performed routinely after the surgery demonstrated homogeneous perfusion to both allografts (Figure 1).

On transfer to the intensive care unit from the operating room, the patient was hemodynamically stable and receiving lung-protective mechanical ventilation with tidal volumes set at 6 ml/kg donor predicted body weight. A chest radiograph showed mild diffuse bilateral infiltrates (Figure 2A).

At 24 hours, the ratio of PaO_2 to the fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) was 215, consistent with moderate primary graft dysfunction (PGD grade 2). On the first postoperative day, routine bronchoscopy showed intact bronchial anastomoses and minimal clear secretions.

The patient was extubated and was subsequently supported with supplement oxygen administered via high-flow nasal cannula (Opti-Flow; Fisher & Paykel Healthcare, Auckland, New Zealand), initially at 0.6 FiO_2 . The FiO_2 was weaned down to 0.45 by the evening of Postoperative Day 1. At that time the estimated $\text{PaO}_2/\text{FiO}_2$ was 207.

Early on the second postoperative day, the patient became progressively more hypertensive, with systolic blood pressures greater than 150 mm Hg. A continuous infusion of nicardipine was initiated. Soon after, the patient developed worsening respiratory failure with tachypnea and increased work of breathing, and her oxygen requirements rose progressively. She was titrated up to an FiO_2 of 1.0 on the high-flow nasal cannula. Arterial blood gas measurement showed normal PCO_2

and pH but severe hypoxemia, with an estimated $\text{PaO}_2/\text{FiO}_2$ of 69 (Table 1). She remained hemodynamically stable.

A focused physical examination was significant for audible breath sounds over both lung fields. Bilateral chest tubes had normal fluctuations in the water-seal chamber with respiratory effort without any air leak. A follow-up chest radiograph showed no acute change (Figure 2B). An electrocardiogram showed no signs of myocardial ischemia.

Figure 1. Perfusion scan immediately after bilateral lung transplantation. Perfusion is identified in bilateral transplanted lungs, with slight heterogeneity of perfusion at the lung base. The right-to-left perfusion ratio based on the anterior view was estimated at 60–40%. These findings suggest intact vascular anastomoses without complications.

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Figure 2. (A) Chest radiograph performed immediately after transplantation, showing mild diffuse bilateral infiltrates, consistent with moderate primary graft dysfunction. (B) Subsequent chest radiograph, showing no acute changes.

Questions

1. What is the most likely cause of this patient's hypoxemia?
2. What is the pathophysiological mechanism?
3. How would you approach management of the hypoxemic respiratory failure in this patient?

[Continue onto next page for answers]

Table 1. Vital signs and other objective data before, during, and after nicardipine infusion

	Postoperative Day 2		
	00:00–01:00 h	03:00–04:00 h	05:00–07:00 h
Temperature, °C	37.1	36.7	36.6
Heart rate, beats/min	85	94	70
BP (mm Hg), SBP/DBP	139/68	136/61	110/57
PAS/PAD	37/13	37/12	28/11
PCWP, mm Hg	13	—	13
CVP, mm Hg	3	8	3
CI (thermodilution), L/min/m ²	2.4	—	2.29
FiO ₂	0.45	1	0.45
pH, arterial	7.39	7.43	7.44
Pco ₂ (arterial), mm Hg	36	39	39
Po ₂ (arterial), mm Hg	93	69	110
PaO ₂ /FiO ₂ ratio	207	69	240
Nicardipine infusion rate, mg/h	0	3	0

Definition of abbreviations: BP = blood pressure; CI = cardiac index; CVP = central venous pressure; DBP = diastolic blood pressure; PAD = pulmonary artery diastolic pressure; PAS = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

Clinical Reasoning

Sudden, severe hypoxemia on the second postoperative day after lung transplantation has a broad differential diagnosis. This includes causes directly related, and indirectly related, to the surgery (Table 2). Directly related causes include PGD, bronchial anastomotic complications, pulmonary venous and arterial vascular anastomotic complications, and cardiac tamponade. Indirectly related causes include pulmonary embolus, pneumothorax, atelectasis, mucus plugging, pneumonia/sepsis, pulmonary edema, and acute myocardial infarction. Table 2 highlights key symptoms and signs of these conditions and the pertinent negative findings relating to the patient in our case vignette.

In the absence of these usual causes of hypoxemia, we considered the relationship between starting nicardipine and the development of rapidly progressive, severe hypoxemia (Table 1). Nicardipine inhibits hypoxic pulmonary vasoconstriction (1–6). Hypoxic pulmonary vasoconstriction is a reflex contraction of vascular smooth muscle in the pulmonary circulation in the setting of alveolar hypoxia. Hypoxic pulmonary vasoconstriction is an important compensatory mechanism to minimize ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatching and shunting that can occur in the situation of heterogeneous or focal pulmonary pathology, as shown in Figure 3. We reasoned that in a patient with PGD, inhibition of hypoxic pulmonary vasoconstriction by nicardipine might be responsible for the acute onset of her severe hypoxemia.

The Clinical Solution

Nicardipine was stopped, and our patient was given furosemide and administered noninvasive mechanical ventilation. Within 1 hour, the FI_{O_2} was reduced from 1.0 to 0.45 and the estimated $\text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2}$ increased from 69 to 240. Over the next few days, allograft function continued to improve, and the patient was weaned to ambient air by Postoperative Day 6.

On the basis of the rapid improvement in the patient's hypoxemia after the discontinuation of nicardipine, we reasoned that inhibition of hypoxic pulmonary vasoconstriction by nicardipine was the main contributor to the severe and rapidly reversible hypoxemic respiratory failure. The underlying heterogeneous/focal pulmonary dysfunction from moderate PGD was a precondition leading to $\dot{V}/\dot{Q}$

Table 2. Differential diagnosis for acute, severe hypoxic respiratory failure in the early post–lung transplantation period

Differential Diagnosis	Typical Presentation	Pertinent Negative Findings in Patient
Directly Related to Surgery		
Primary graft dysfunction	Diffuse alveolar infiltrates on CXR with hypoxemic respiratory failure	CXR with no change in mild diffuse infiltrates
Pulmonary venous anastomotic obstruction	Pulmonary edema refractory to diuresis on the site of anastomotic problem	Responded to diuresis
Pulmonary arterial anastomotic obstruction	Pulmonary hypertension, signs of right heart failure, systemic hypotension	CVP normal, PA pressures normal, systemic hypertension
Bronchial anastomotic dehiscence	Substantial air leak from chest tube	No air leak from the chest tube
Phrenic nerve injury	Hypoventilation, CXR reveals atelectasis or hemidiaphragm elevation	Normal Pco_2 . Negative for these findings on CXR
Torsion of the allograft	Acute pulmonary hypertension, CXR with alveolar infiltrates with consolidation	Normal PA pressures, CXR without these findings
Hyperacute rejection/acute rejection	Nonspecific findings of fever, cough, shortness of breath. Progressively worsening alveolar infiltrates on the CXR	Rapid clinical improvement without specific treatment for acute rejection
Cardiac tamponade	Elevated CVP, systemic hypotension, equalization of diastolic pressures, low cardiac index	Normal CVP, systemic hypertension, cardiac index within normal limits
Indirectly Related to Surgery		
Pneumonia/sepsis	Fever, abnormal lobar infiltrate	No fever, no lobar infiltrate on CXR
Aspiration	Focal pulmonary alveolar infiltrates on CXR	No focal pulmonary alveolar infiltrates on CXR
Volume overload	Diffuse fluffy infiltrates, elevated CVP, elevated filling pressures	Only mild diffuse infiltrates, normal filling pressures
Mucus plugging/atelectasis	Opacity of a segment or part of the lung	No focal opacity seen on CXR. Bronchoscopy 24 h previously with patent airways
Pulmonary embolism	Tachycardia, systemic hypotension if massive, pulmonary hypertension	No tachycardia. Systemic hypertension. No pulmonary hypertension
Myocardial infarction	EKG changes, troponin elevation	No ischemic EKG changes, negative troponins
Cardiac shunt (PFO)	Hypoxemia unresponsive to increasing FI_{O_2}	No PFO on pretransplantation TTE with bubble study or intraoperative TEE
Methemoglobinemia	Cyanosis, blood shows chocolate-brown color. Dysmethemoglobinemia: Sp_{O_2} low, Pa_{O_2} is normal or high	No cyanosis, no dysmethemoglobinemia
TRALI	Lung injury after blood product exposure	No blood product exposure

Definition of abbreviations: CXR = chest radiograph; CVP = central venous pressure; PA = pulmonary artery; PFO = patent foramen ovale; Sp_{O_2} = arterial oxyhemoglobin saturation; TEE = transesophageal echocardiogram; TRALI = transfusion-related acute lung injury; TTE = transthoracic echocardiogram.

Figure 3. Effects of ventilation-perfusion ($\dot{V}/\dot{Q}$) relationships on oxygen exchange in a two-compartment lung under (A) ideal or perfect conditions, (B) $\dot{V}/\dot{Q}$ mismatch (absent ventilation in one compartment with $\dot{V}/\dot{Q} = 0$, consistent with right-to-left shunt) with hypoxic pulmonary vasoconstriction, (C) $\dot{V}/\dot{Q}$ mismatch (absent ventilation in one compartment with $\dot{V}/\dot{Q} = 0$, consistent with right-to-left shunt) without hypoxic pulmonary vasoconstriction, and (D) $\dot{V}/\dot{Q}$ mismatch (absent ventilation in one compartment with $\dot{V}/\dot{Q} = 0$, consistent with right-to-left shunt) without hypoxic pulmonary vasoconstriction in the setting of low mixed venous P_{O_2} . Values for total ventilation ($\dot{V}$), inspired oxygen tension ($P_i O_2$), total cardiac output ($\dot{Q}$), and mixed venous oxygen concentration ($C_{mv} O_2$), tension ($P_{mv} O_2$), and hemoglobin saturation ($S_{mv} O_2$) shown in (A) were the same for all conditions, except for (D), as indicated. Compartmental ventilation ($\dot{V}_1$, $\dot{V}_2$), perfusion ($\dot{Q}_1$, $\dot{Q}_2$), ventilation-perfusion ratio ($\dot{V}_1/\dot{Q}_1$, $\dot{V}_2/\dot{Q}_2$), the resulting systemic arterial oxygen concentration ($C_a O_2$), calculated as the perfusion-weighted mean of the oxygen concentrations in blood flowing from each compartment), and corresponding systemic arterial oxyhemoglobin saturation ($S_a O_2$) and oxygen tension ($P_a O_2$) are also indicated for each condition. For simplicity, oxygen concentrations were calculated as the product of hemoglobin concentration (15 g/dl), hemoglobin oxygen-binding capacity (1.34 vol% per g/dl), and oxyhemoglobin saturation, and ignore the concentration of oxygen physically dissolved in plasma, which would be small at these oxygen tensions. Vol% indicates milliliters of oxygen (STPD) per 100 ml of blood. Reproduced by permission from Reference 1. HPV = hypoxic pulmonary vasoconstriction.

mismatch. Nicardipine, by inhibiting hypoxic pulmonary vasoconstriction, likely caused severe worsening of the $\dot{V}/\dot{Q}$ mismatch and shunting in the most dysfunctional pulmonary units.

The Science behind the Solution

What Is Hypoxic Pulmonary Vasoconstriction, and Why Is It Useful?

Hypoxic pulmonary vasoconstriction is a reflex contraction of vascular smooth muscle cells in both the arterioles and venules of the lungs, initiated by a reduction in local P_{O_2} engendered in most settings by alveolar hypoxia (1, 2). Because it is not

solely dependent on autonomic input, hypoxic pulmonary vasoconstriction is still present in the denervated, transplanted lung (3), similarly as in a normal lung.

Hypoxic pulmonary vasoconstriction is fundamentally different from the response to hypoxia in the systemic circulation, which typically leads to vasodilation. In 1946 von Euler and Liljestrand were the first to suggest that hypoxic pulmonary vasoconstriction leads to “an adequate distribution of the blood through the various parts of the lungs according to the efficiency of ventilation” (4). They proposed that hypoxic pulmonary vasoconstriction is a mechanism that optimizes oxygenation of blood in the lung by matching local perfusion to local ventilation.

Hypoxic pulmonary vasoconstriction is modulated by carbon dioxide (5). The presence of hypercapnia with acidosis augments hypoxic pulmonary vasoconstriction and can further improve ventilation and perfusion matching (5, 6). Thus, a key function of hypoxic pulmonary vasoconstriction is to reduce the impact of $\dot{V}/\dot{Q}$ mismatch on gas exchange, as shown in Figure 3.

In Figure 3 the lung is shown as a simple two-compartment model (1). Figure 3A shows an ideal or perfect lung breathing ambient air with matched ventilation and perfusion in both compartments ($\dot{V}/\dot{Q} = 1$), with a resulting arterial P_{O_2} of 100 mm Hg and an arterial oxyhemoglobin saturation of 98%. In Figure 3B one compartment is shown with

completely obstructed airflow and absence of alveolar ventilation. With hypoxic pulmonary vasoconstriction intact, a reduced perfusion of the obstructed compartment occurs. In this example the blood flow to the obstructed compartment is, via hypoxic pulmonary vasoconstriction, reduced from 2.5 to 1 L/min (60% reduction).

Because of the blood flow diversion, via hypoxic pulmonary vasoconstriction in the obstructed compartment, the perfusion to the nonobstructed compartment increases. The nonobstructed, well-ventilated compartment now receives 80% of the total blood flow and maintains a $\dot{V}/\dot{Q}$ of 1.25, whereas the obstructed compartment with a $\dot{V}/\dot{Q}$ of 0 receives only 20% of the total blood flow (Figure 3B). Thus, despite a $\dot{V}/\dot{Q}$ of 0 in one of the two compartments, the arterial P_{O_2} is preserved at 68 mm Hg and an arterial oxyhemoglobin saturation of 93%.

Figure 3C again shows one compartment with completely obstructed airflow and absence of alveolar ventilation; however, it now demonstrates the effect of absent hypoxic pulmonary vasoconstriction. Thus, with equal blood flow from each compartment, the arterial P_{O_2} is reduced to 52 mm Hg and an arterial oxyhemoglobin saturation of 87% (Figure 3C).

The impact of a falling mixed venous P_{O_2} , which will occur as arterial saturation and oxygen content fall, is shown in Figure 3D. It again shows one compartment with completely obstructed airflow and the absence of alveolar ventilation. It demonstrates the greater effect of absent hypoxic pulmonary vasoconstriction in the setting of a low mixed venous P_{O_2} of 26.6 mm Hg (oxyhemoglobin saturation of 50%). Again, with equal blood flow from each compartment because of the absent hypoxic pulmonary vasoconstriction, there is a greater reduction in arterial P_{O_2} , now to 40 mm Hg, and the arterial oxyhemoglobin saturation is reduced now to 75%.

Cellular Mechanisms of Hypoxic Pulmonary Vasoconstriction

The ability of small pulmonary vessels to contract in response to hypoxia resides in the pulmonary arterial smooth muscle cells (1). The three important components of pulmonary arterial smooth muscle cells involved in mediating hypoxic pulmonary

vasoconstriction are as follows: the cell membrane, the sarcoplasmic reticulum, and the contractile apparatus.

At the smooth muscle cell membrane, hypoxic pulmonary vasoconstriction has been postulated to be mediated through L-type voltage-gated calcium channels. At resting membrane potential (about -60 mV) these calcium channels are mostly closed. Hypoxia inhibits outward potassium current causing membrane depolarization (Figure 4) (7). If hypoxia-mediated cell membrane depolarization occurs, the L voltage-gated calcium channels open, causing the entry of calcium, which then leads to further release of calcium from the sarcoplasmic reticulum. The intracellular release of calcium activates

the contractile apparatus, leading to vasoconstriction. Inhibition of potassium current and subsequent cell membrane depolarization is proportional to the severity of hypoxia and is more prominent in the smaller, low-resistance arteries than in the larger pulmonary arteries (7).

Pharmacologic Inhibition of Hypoxic Pulmonary Vasoconstriction

Inhibition of hypoxic pulmonary vasoconstriction by calcium channel blockers was demonstrated in the isolated lung and in animal models (8). Nicardipine is a potent inhibitor of hypoxic pulmonary vasoconstriction (Figure 5) (8). Simonneau and colleagues demonstrated that

Figure 4. The role of K^+ channels and voltage-dependent Ca^{2+} channels in membrane depolarization (membrane potential, E_m) and pulmonary vasoconstriction. When K^+ channels are closed, the resulting membrane depolarization opens voltage-dependent Ca^{2+} channels (VDCCs), promotes Ca^{2+} influx, increases $[Ca^{2+}]_{cyt}$, and causes vasoconstriction. When K^+ channels are activated the resulting membrane hyperpolarization closes VDCCs, inhibits agonist-mediated Ca^{2+} influx, and causes vasodilation. $[Ca^{2+}]_{cyt}$ = Ca^{2+} concentration in the cytosol; PASMC = pulmonary artery smooth muscle cell. Reproduced by permission from Reference 4.

Figure 5. Pulmonary vascular resistance (PVR) during left lower lobe (LLL) normoxia and LLL hypoxia with and without nicardipine at 1, 3 or 6 μg/kg/min. Data are expressed as means ± SEM (n = 7). Significant change from LLL normoxia at same dose of nicardipine: ††*P* < 0.01. Significant change from control LLL hypoxia: §§*P* < 0.01. Reproduced by permission from Reference 8.

nifedipine, a potent calcium channel blocker, inhibits hypoxic pulmonary vasoconstriction in humans with respiratory disease from chronic airflow obstruction (9). Nifedipine also caused a significant lowering of arterial PO_2 from 45 ± 2 to 42 ± 2 mm Hg (*P* < 0.01) (7).

This was, however, compensated by the increased cardiac output caused by the systemic vasodilatory effect of nifedipine, so that the quantity of oxygen transported per unit of time by the arterial blood actually rose slightly (*P* < 0.05).

Table 3. Pharmacologic inhibition of hypoxic pulmonary vasoconstriction

Vasoactive Drug	Effect on Hypoxic Pulmonary Vasoconstriction
Calcium channel blockers	Animal and human studies → impair hypoxic pulmonary vasoconstriction. Nifedipine is used treat and prevent HAPE in humans
Acetazolamide	Animal and human studies → impair hypoxic pulmonary vasoconstriction
Sodium nitroprusside	Vasodilator → impairs hypoxic pulmonary vasoconstriction
Nitroglycerine	Vasodilator → impairs hypoxic pulmonary vasoconstriction
Phosphodiesterase inhibitors	Attenuate hypoxic pulmonary vasoconstriction response. Sildenafil in particular is used to prevent HAPE and in the treatment of pulmonary arterial hypertension
ACE inhibitors	Reduce hypoxic pulmonary vasoconstriction
Endothelin antagonists	Attenuate hypoxic pulmonary vasoconstriction. Drugs such as bosentan and sitaxsentan
Halothane	Potent inhibitor of hypoxic pulmonary vasoconstriction
Hydralazine	Vasodilator → impairs hypoxic pulmonary vasoconstriction
Angiotensin receptor blockers	Reduce hypoxic pulmonary vasoconstriction
Leukotriene antagonists and receptor blockers	Inhibitors of hypoxic pulmonary vasoconstriction
β ₂ -Receptor agonists	Attenuate hypoxic pulmonary vasoconstriction

Definition of abbreviations: ACE = angiotensin-converting enzyme; HAPE = high-altitude pulmonary edema.

Because of the increased oxygen delivery from the increased cardiac output the mixed venous PO_2 was unchanged by nifedipine (baseline, 30 ± 1 mm Hg; during nifedipine, 30 ± 2 mm Hg). Without the effect on the systemic circulation, the lower arterial PO_2 caused by nifedipine would have also lowered the mixed venous PO_2 , and this would have increased the fall in arterial oxygen tension caused by nifedipine, as highlighted in Figure 3D.

There are several case reports of calcium channel blocker-induced hypoxemia in patients with underlying pulmonary pathology. However, we are not aware of previous case reports of hypoxemia caused by administration of a calcium channel blocker to a patient who had undergone lung transplantation. There are two reports of nimodipine-induced acute hypoxemia in patients with traumatic subarachnoid hemorrhage complicated by respiratory failure (10, 11). In addition, there is a report of a 55-year-old man with moderate hypoxemic respiratory failure from lobar pneumonia, who presented with substantial worsening of his hypoxemia after intravenous administration of nicardipine (12), as in our patient.

In addition to calcium channel blockers, there are a number of other vasoactive drugs that can inhibit hypoxic pulmonary vasoconstriction (Table 3). Vasodilators, like sodium nitroprusside, can inhibit hypoxic pulmonary vasoconstriction. A report on a 61-year-old patient with chronic obstructive pulmonary disease undergoing mitral valve repair showed a temporal relationship between starting sodium nitroprusside and severe hypoxemia (13). This report highlighted that low mixed-venous oxyhemoglobin saturations amplify the effect of pharmacologic inhibition of hypoxic pulmonary vasoconstriction (Figure 3D).

Conclusion

Hypoxic pulmonary vasoconstriction is an important mechanism to optimize oxygenation of blood in the lung by matching local perfusion to local ventilation. Inhibiting hypoxic pulmonary vasoconstriction in the setting of heterogeneous or focal pulmonary pathology can increase shunt flow and $\dot{V}/\dot{Q}$ mismatch and contribute to significant

worsening of hypoxemic respiratory failure. This case highlights that pharmacologic inhibition of hypoxic pulmonary vasoconstriction is an important consideration in the differential diagnosis of hypoxemia.

Answers

1. What is the most likely cause of this patient's hypoxemia?

Sudden, severe hypoxemia on the second postoperative day after lung transplantation

has a broad differential diagnosis, which includes causes directly related, and indirectly related, to the surgery, as detailed in Table 2.

2. What is the pathophysiological mechanism?

On the basis of the rapid improvement in the patient's hypoxemia after the discontinuation of nicardipine, we reasoned that inhibition of hypoxic pulmonary vasoconstriction by nicardipine was the main contributor to the severe and rapidly reversible hypoxemic respiratory failure.

3. How would you approach the management of the hypoxemic respiratory failure in this patient?

Nicardipine was stopped to restore hypoxic pulmonary vasoconstriction, and our patient was given furosemide and administered noninvasive mechanical ventilation to improve the underlying heterogeneous/focal pulmonary dysfunction from moderate primary graft dysfunction. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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