Quantification of oxygen exchange inefficiency in interstitial lung disease

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BACKGROUND

Hypoxemia (low PaO_2) is a hallmark of moderate-to-severe interstitial lung disease (ILD). Ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch is a dominant mechanism, with a secondary role for diffusion limitation (at least at rest).[1] In some patients, intrapulmonary shunting and impaired alveolar exchange of oxygen (O_2) can occur ("physiological" shunt [$Shunt_{PHYS}$]),[2] leading to severe, irreversible or nearly irreversible hypoxemia. Because of the effect of gravity on pulmonary blood flow, any shunted fraction can increase in the upright position when extensive alveolar filling is present in dependent areas of the lung in the setting of relatively preserved capillary perfusion.

OVERVIEW

A 23-year-old woman reported progressive dyspnea and dry cough for a few months after an acute episode of fever and sore throat. On examination, she assumed the supine position (SpO_2 = 96% on room air), reporting dyspnea soon after sitting (platypnea); of note, her SpO_2 was consistently < 88% when she was in the upright position (orthodeoxia).[3] No environmental exposures were identified; however, she reported chronic use of nitrofurantoin for urinary tract infections. COVID-19 and HIV testing was negative, as was liver and connective tissue disease workup. Spirometry in the recumbent position (≈30°) revealed severe and proportional reductions in FEV_1 and FVC (Figure 1A). Arterial blood gas analysis after administration of 100% O_2 for 20 min revealed increased right-to-left shunt that almost doubled from the supine to the seated position (Figure 1B). Chest CT showed extensive ground-glass/reticular opacities, septal thickening, and traction bronchiectasis/bronchiolectasis, particularly in the anterior aspects of the lower lobes and in the right middle lobe/lingula (indeterminate usual interstitial pneumonia; Figure 1C). Transesophageal echocardiography

(A)

	Pre-BD	% predicted	Post-BD	% predicted
FVC (L)	1.06	29	0.90	25
FEV_1 (L)	1.05	34	0.74	24
FEV_1/FVC	0.99		0.82	

(B)

	Supine	Supine	Seated
Barometric pressure		760 mmHg (sea level)	
FiO_2	21	100	100
pH	7.43	7.42	7.39
$PaCO_2$ (mmHg)	41.5	47.2	44.6
HCO_3 (mmol/L)	27.7	30.0	26.7
PaO_2 (mmHg)	63.7	510.0	374.0
SaO_2 (%)	94.3	100	100
Estimated PAO_2 (mmHg)	NA	654.0	657.2
Estimated shunt (%)	NA	7.9	14.5

(C)

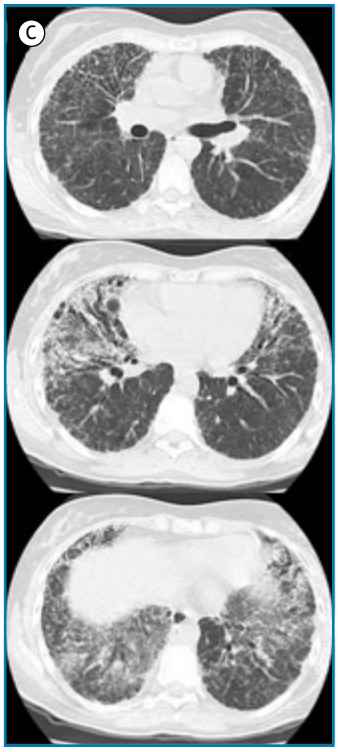

Figure 1. Spirometry (in A), arterial blood gas analysis (in B), and chest CT (in C) in a 23-year-old woman with complaints of progressive dyspnea following chronic nitrofurantoin use. In addition to severe restriction on spirometry and interstitial lung disease with craniocaudal distribution, right-to-left shunt measured during 100% O_2 breathing was increased in the supine position, further increasing in the upright position. BD: bronchodilator; HCO_3: bicarbonate; and PAO_2 = alveolar partial pressure of O_2.

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showed no structural cardiac abnormalities; however, microbubbles appeared in the left chambers every 3-8 beats after their identification in the right atrium (i.e., intrapulmonary shunt).[3] CT pulmonary angiography revealed no pulmonary embolism or arteriovenous malformations.

$Shunt_{PHYS}$ (venous admixture; normal ≤ 10%) can be subdivided into: a) anatomic shunt ($Shunt_{ANAT}$) via bronchial, pleural, and thebesian veins (normal ≤ 5%); b) capillary shunt ($Shunt_{CAP}$), representing pulmonary capillary blood in contact with completely unventilated alveoli; and c) shunt effect (i.e., perfusion in excess of ventilation).[2] Unlike the alveolar-arterial O_2 gradient,[4] $Shunt_{PHYS}$ is independent of the shape of the O_2 dissociation curve, but it requires sampling pulmonary arterial blood to obtain mixed venous oxygen content. Making the subject breathe pure O_2 for sufficient time to wash out nitrogen allows the measurement of the fraction of venous admixture caused by $Shunt_{ANAT}$ plus $Shunt_{CAP}$ (i.e., "absolute shunt") without the confounding influence of $\dot{V}/\dot{Q}$ inequalities.[2] When intracardiac communication, pulmonary arteriovenous malformations, and hepatopulmonary syndrome are excluded as causes of orthodeoxia in ILD patients, other possible causes include increased $Shunt_{CAP}$ and undetected small arteriovenous channels (≤ 20 μm diameter).[5] The supine position increases venous return, which is more homogenously distributed to better ventilated areas (superior and posterior lung fields in the present case; Figure 1C), reducing the shunted fraction and improving oxygenation and dyspnea.[3]

CLINICAL MESSAGE

Platypnea-orthodeoxia is a potential cause of atypical/paroxysmal dyspnea and refractory hypoxemia in ILD patients in the upright position. Quantification of postural modifications in "absolute shunt" measured during 100% O_2 breathing provides a minimally invasive test of O_2 exchange efficiency that is dependent on changes in regional lung perfusion.

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