# Dynamic right-to-left interatrial shunt may complicate severe COVID-19

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#### SUMMARY

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**To cite:** Rajendram R, Hussain A, Mahmood N, *et al. BMJ Case Rep* 2021;**14**:e245301. doi:10.1136/bcr-2021-245301 Right-to-left (RTL) interatrial shunt (IAS) may complicate select cases of COVID-19 pneumonia. We describe the use of serial imaging to monitor shunt in critically ill patients. A 52-year-old man presented with COVID-19 pneumonia. Hypoxia worsened despite maximal medical therapy and non-invasive ventilation. On day 8, saline microbubble contrast-enhanced transthoracic echocardiography revealed a patent foramen ovale (PFO) with RTLIAS. Invasive ventilation was initiated the next day. The course was complicated by intermittent severe desaturation without worsening aeration or haemodynamic instability, so PFO closure was considered. However, on day 12, saline microbubble contrast-enhanced transoesophageal echocardiography excluded RTLIAS. The patient was extubated on day 27 and discharged home 12 days later. Thus, RTLIAS may be dynamic and changes can be detected and monitored by serial imaging. Bedside echocardiography with saline microbubble contrast, a simple, minimally invasive bedside test, may be useful in the management of patients with severe hypoxia.

## BACKGROUND

There is significant heterogeneity in the respiratory phenotype of COVID-19.<sup>12</sup> The pathogenesis is complex and is still being elucidated. It differs from other causes of hypoxic respiratory failure in that ongoing viral activity within already damaged tissues can cause a spectrum of anatomically and temporally distinct pathologies.<sup>3</sup> These include tracheobronchitis, diffuse alveolar damage and vascular injuries.<sup>3</sup>

Thus, COVID-19 involves, to a variable extent, loss of aeration, dysregulation of pulmonary vascular tone and microvascular thrombosis.<sup>3 4</sup> Pulmonary embolism is also common.<sup>3 4</sup> These thrombi should increase dead space. However, a series of critically ill patients with acute respiratory distress syndrome induced by COVID-19 had a significant right-to-left (RTL) shunt despite relatively normal lung compliance.<sup>1</sup> Indeed, it has been demonstrated that both intrapulmonary shunt and acute RTL interatrial shunt (IAS) can contribute to hypoxia in COVID-19.<sup>5 6</sup>

The sequelae of COVID-19 can induce or exacerbate pulmonary hypertension and thereby precipitate RTLIAS.<sup>6–8</sup> The standard approach to the management of hypoxia may also worsen RTLIAS.<sup>6–9</sup> However, no previous reports have described the use of serial imaging to monitor changes in RTLIAS. We describe the use of saline microbubble contrast-enhanced echocardiography

to demonstrate that, when present in patients with COVID-19, IAS may be dynamic.

#### **CASE PRESENTATION**

A 52-year-old man with no medical history presented with fever, cough and breathlessness due to COVID-19. His oxygenation gradually deteriorated despite treatment with antibiotics, dexamethasone and tocilizumab (table 1). Eight days after admission, he developed acute severe hypoxia (oxygen saturation (SpO<sub>2</sub>) 85%; arterial oxygen pressure 54 mm Hg) despite high-flow nasal oxygen (fractional inspired oxygen (FiO<sub>2</sub>) 0.7, 60 L/min). Oxygenation initially improved with awake prone positioning.

#### INVESTIGATIONS

Table 1 correlates the patients' inflammatory markers, blood gases and treatment over the course of his illness. The chest X-ray on admission (figure 1) revealed bilateral patchy interstitial oedema, and COVID-19 PCR was positive. On day 8, the infiltrates on the chest X-ray had worsened (figure 2) and lung ultrasound revealed bilateral patchy B-pattern. However, the degree of aeration loss shown by imaging was not thought to be sufficient to explain the severity of the hypoxaemia, so additional diagnoses were considered.

The D-dimer was raised (9.65 mg/L), but clinical instability initially precluded CT. However, bedside ultrasound excluded deep vein thrombosis and acute cor pulmonale. Sputum cultures were negative. The patient's ECG was unremarkable and although his heart appeared normal on transthoracic echocardiography (TTE), fixed bowing of the interatrial septum to the left (video 1) suggested that the right atrial (RA) pressure was greater than the left atrial (LA) pressure. Saline microbubble contrast-enhanced TTE also demonstrated a patent foramen ovale (PFO) with RTLIAS (figure 3 and video 1).

Thereafter, it was noted that, despite unchanged aeration and haemodynamic conditions, the SpO<sub>2</sub> intermittently fell below 80%. Each of these episodes triggered an assessment by a physician and a series of interventions (described below). So, the arterial blood gas analyses presented in table 1 reflect the oxygenation after adjustment of respiratory support. For example, on day 9, the patient was positioned prone when oxygenation did not improve significantly after endotracheal ventilation and initiation of mechanical ventilation. The arterial blood gas analyses, performed at 04:40 on day 10 and 03:40 on day 12, reflect the improvement in

Table 1 Ti	meline correlà	ating arterial l	blood gas	es and resp.	iratory suppc	ort with selec	t investigations	and treatm	nent							
Day	0	-	2	2	3	3	8	8	6	10	11	11	12	27	33	39
Time	10:00	01:10	10:20	14:10	08:25	20:00	12:50	21:20	15:50	04:40	04:10	16:30	03:40	12:40	17:10	10:00
Intervention	COVID-19 PCR positive	07:00 steroid started				Day 4 15:00 tocilizumab given	15:00 TTE PFO and RTLIAS anticoagulated		13:00 tracheal intubation				13:00 TOE no RTLIAS	Tracheal extubation		Home
Lymphocytes, ×10 <sup>9</sup> /L	0.67	0.92	0.79		0.53				0.65		0.73				2.45	
CRP, mg/L		76	70		39		7			17					27	
Ferritin, µg/L		1847	2925		1979		785			892						
D-dimer, mg/L		0.54	0.55		0.74		9.65			1.95					1.12	
LDH, U/L			791		901		1167				726					
<b>S</b> pO <sub>2</sub> , %	94	91	93	90	92	91	84	94	91	98	86	92	95	92	95	95
RR, breaths/ min	24	29	29	30	36	35	29	28	24	32	30	30	30	32	22	21
Position	Sitting	Sitting	Sitting	Sitting	Sitting	Prone	Sitting	Prone	Supine	Prone	Supine	Supine	Prone	Sitting	Sitting	
Respiratory support		NC	FM	NRB FM	NRB FM	HFNC	HFNC	Helmet BiPAP	ETT VC+	ETT VC AC	ETT VCAC	ETT VC AC	ETT VC AC	HFNC	NC	
FIO <sub>2</sub>	0.21					0.35	0.7	1.0	1.0	0.6	0.5	0.5	0.4	0.5		0.21
Flow, L/min		-	10	12	15	40	60	60	60	60	50	50	50	50	1.5	
PEEP, cmH <sub>2</sub> 0								10	14	14	12	12	10			
Peak AP, cmH <sub>2</sub> 0								16	35	34	38	37	35			
VT, mL									450	325	441	437	438			
Compliance, mL/cmH <sub>2</sub> 0*									21.4	16.3	17.0	17.5	17.5			
Н			7.46	7.45	7.46		7.49	7.45	7.28	7.24	7.37	7.491	7.51	7.5	7.49	
PaCO <sub>2</sub> , mm Hg			35	37	35		31	35	49	66	51	39.8	37	41	36	
BE, mmol/L			1.1	1.3	1.2		0.6	0.2	-4.2	-1.2	2.6	9	5.6	7.6	3.6	
PaO <sub>2</sub> , mm Hg			52	57	62		43	67	71	97	71	57.6	68	78	<b>6</b> 6	
PaO <sub>2</sub> /FiO <sub>2</sub>							51	67	71	162	142	115	171	155		
Timeline correla presented reflec blood gas analy: *Dynamic compl VC AC, volume c dehydrogenase; saturation: TOF	ting arterial blood t the patient's oxy ses, performed at 1 liance was calcula ontrol-assist contr NC, masal canula transoesconhageal	gases and respira genation after adj 24:40 on day 10 a ted. ol; Peak AP, peak ; NRB, non-rebrea	itory support lustment of r nd 03:40 on airway press the: PaCO <sub>2</sub> , <i>i</i> r.TTE, transf	t with select inw espiratory supp day 12, reflect day 12, base ex ure; BE, base ex arterial carbon c horacic echocar	estigations and t ort. For example, the improvement cess; BiPAP, bile, lioxide pressure; diooraphy: VC+.	reatment. Althou , on day 9, oxyge t in oxygenation vel positive airwé PaO <sub>2</sub> , arterial oxy volume control n	gh SpO <sub>2</sub> intermittentl nation did not improv after several hours of sy pressure; CRP, C re. ygen pressure; PEEP, I duts. VT ridal volume.	y fell below 80 /e significantly prone position active protein; positive end ev	)%, each incide after endotrach ning and reduct ETT, endotrache piratory pressu	nt triggered an neal ventilation ion of PEEP. sal tube; FiO <sub>2</sub> , fi re; PFO, patent	assessment by and initiation o and initiation o actional inspire foramen ovale;	a physician a f mechanical d oxygen; FN RR, respirato	nd a series of in ventilation so t 1, face mask; HF ry rate; RTLIAS, I	terventions. So, the he patient was poo NC, high-flow nasi right-to-left interai	e arterial blood sitioned prone. al cannula; LDH trial shunt; SpO	gas analyses The arterial , lactate , oxygen
VC AC, volume c dehydrogenase; saturation; TOE,	control-assist cont. NC, nasal cannula transoesophageal	rol; Peak AP, peak ı; NRB, non-rebrea echocardiography	airway press the; PaCO <sub>2</sub> , ¿ /; TTE, transti	sure; BE, base ex arterial carbon c horacic echocar	ccess; BiPAP, blie Jioxide pressure; diography; VC+,	vel positive airwa PaO <sub>2</sub> , arterial ox volume control p	ay pressure; CKP, C rei ygen pressure; PEEP, I ilus; VT, tidal volume.	active protein; positive end e>	EIT, endotrache ¢piratory pressu	eal tube; HO <sub>2</sub> , 11 re; PFO, patent	'actional ınspıre foramen ovale;	d oxygen; FN RR, respirato	1, tace mask; HF ry rate; RTLIAS, I	NC, high-tlow nas right-to-left interat		ai cannula; LDH irial shunt; SpO



**Figure 1** Chest X-ray on admission. Chest X-ray demonstrating bilateral patchy alveolar infiltrate.

oxygenation after several hours of prone positioning and reduction of positive end expiratory pressure (PEEP).

Percutaneous closure of the PFO was considered. However, on day 12, saline microbubble contrast-enhanced transoesophageal echocardiography (TOE), performed while the patient was supine, demonstrated absence of RTLIAS (figure 4 and video 2). Bowing of the interatrial septum to the right with mid-systolic buckling (video 2) suggested that the pulmonary capillary wedge pressure (PCWP) and the pressure gradient between the LA and the RA had normalised. On day 20, CT pulmonary angiography (CTPA) demonstrated consolidation, diffuse ground-glass opacities and small pleural effusions but excluded pulmonary emboli.



**Video 1** Intravenous microbubble contrast-enhanced transthoracic echocardiographic study demonstrating right-to-left interatrial shunt. Labelled 2D subcostal four-chamber echocardiographic recording of the heart after intravenous injection of saline microbubble contrast demonstrating grade 2 shunt (5–25 bubbles). Fixed bowing of the interatrial septum to the left suggests that the right atrial (RA) pressure is greater than the left atrial (LA) pressure. Bubbles appearing in the LA within three cardiac cycles of opacification of the RA demonstrate the presence of a right-to-left interatrial shunt.

#### **DIFFERENTIAL DIAGNOSIS**

Although the patient was diagnosed with COVID-19 pneumonia, he deteriorated suddenly 8 days after admission. The aetiology of the hypoxaemia was thought to be multifactorial. While COVID-19 had caused significant lung injury, the severity of the changes on chest X-ray (figure 2) and lung ultrasound was not thought to be sufficient to explain the severity of the patient's hypoxaemia (table 1). Pulmonary emboli, mucus plugging and superimposed bacterial infection were considered. However, CTPA and respiratory cultures were subsequently negative.

Oxygenation improved with prone positioning but not with dorsal recumbency. So, diagnostic criteria for platypnoea– orthodeoxia were not fulfilled. Regardless, the presence of relevant RTLIAS using saline microbubble contrast-enhanced



**Figure 2** Chest X-ray on day 8. Chest X-ray demonstrating worsening bilateral patchy alveolar infiltrate in comparison with the chest X-ray performed on admission (figure 1).



**Figure 3** Transthoracic echocardiography (TTE) demonstrating rightto-left interatrial shunt in a patient receiving high-flow nasal oxygen. (A) Labelled 2D apical four-chamber TTE view of the heart. (B) Labelled 2D apical four-chamber TTE view of the heart after intravenous injection of saline microbubble contrast demonstrating grade 2 shunt (5–25 bubbles in LA). Bubbles appeared in the LA within three cardiac cycles of opacification of the RA demonstrating the presence of a right-to left interatrial shunt. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.



**Figure 4** Transoesophageal echocardiography (TOE) excluding rightto-left interatrial shunt. TOE demonstrating right-to-left interatrial shunt in a patient receiving high-flow nasal oxygen. (A) Labelled 2D mid-oesophageal bicaval TOE view of the heart. (B) Labelled 2D midoesophageal bicaval TOE view of the heart after intravenous injection of saline microbubble contrast demonstrating grade 2 shunt (5–25 bubbles in LA). Bubbles appeared in the LA within three cardiac cycles of opacification of the RA demonstrating the presence of a right-to left interatrial shunt. LA, left atrium; RA, right atrium.

echocardiography on day 8 suggested that this shunt contributed to the patient's severe hypoxaemia. The subsequent observation that this RTLIAS had resolved on day 12, paralleling an improvement in oxygenation and normalisation of the transatrial pressure gradient, demonstrates that RTLIAS, when present, may be dynamic. Thus, intermittent reversal of IAS may have contributed to the episodic, sudden, severe desaturation.

## TREATMENT

In view of the sudden severe deterioration on day 8, the dose of enoxaparin was increased to provide therapeutic anticoagulation, and antibiotic therapy was escalated to include meropenem and vancomycin. The next day, the ratio of  $\text{SpO}_2/\text{FiO}_2$  to respiratory rate (ROX) index fell (3.04).

Improvements in oxygenation with incentive spirometry, chest physiotherapy and awake prone positioning were only sustained for a few hours and the patient began to fatigue. Thus, on day 9, when a trial of non-invasive ventilation via a helmet interface failed, invasive mechanical ventilation was initiated. This initially seemed to improve oxygenation, but the  $FiO_2$  could not be reduced below 1.0 and sudden, severe deoxygenation still





occurred intermittently. Prone positioning allowed some reduction of supplemental oxygen and ventilatory support. However, these improvements in oxygenation were not sustained when the patient was turned supine. So several 'doses' of prone positioning were administered.

The RTLIAS via the PFO was thought to be exacerbating the hypoxaemia caused by COVID-19 pneumonia. So, percutaneous closure of the PFO was considered. However, pending the decision, the oxygenation became more stable (table 1; 3 days later SpO<sub>2</sub> 95%, FiO<sub>2</sub> 0.4, PEEP 10 cmH<sub>2</sub>0, peak airway pressure 35 cmH<sub>2</sub>0). Although the RTLIAS may have been dynamic, the TOE performed on day 12 demonstrated that it had then resolved. Thus, as the patient's oxygenation was improving, a multidisciplinary team including an internist, cardiologist, neurologist and intensivist agreed that current guidelines did not support closure of the patient's PFO.

## **OUTCOME AND FOLLOW-UP**

The patient gradually improved and ventilatory support was weaned. On day 20, anticoagulation was reduced to a prophylactic dose after the CTPA excluded pulmonary emboli. The patient was extubated 18 days after tracheal intubation (ie, day 27). Although rehabilitation was required, the patient was ultimately discharged home 39 days after his initial presentation.

## DISCUSSION

Intrapulmonary shunt and acute RTLIAS are known to contribute to hypoxia in COVID-19.<sup>56</sup> However, no previous reports have described the use of serial imaging to guide management based on changes in shunt. The present case illustrates that when present, RTLIAS may be dynamic. It can improve as COVID-19 resolves.

In the present case, oxygenation improved with prone positioning but not dorsal recumbency. While diagnostic criteria for platypnoea–orthodeoxia syndrome (POS) were not fulfilled, prone positioning may reduce RTLIAS.<sup>10</sup> Yet, although microbubble contrast-enhanced transcranial Doppler ultrasound demonstrated that a large RTLIAS decreased significantly on proning,<sup>10</sup> the precise mechanism for this remains uncertain. In the prone position, the dependent heart rests on the sternum. This change in the position of the heart relative to the vena cavae may divert blood flow away from the PFO.<sup>10</sup> Improvement in lung recruitment, hypoxia, pulmonary vascular resistance and right heart function on proning<sup>11</sup> may also be relevant.

Precise measurement of atrial pressures and the contributions of intrapulmonary shunt (IPS) and extrapulmonary shunt to the total RTL shunt require left and right heart catheterisation. However, this is invasive and impractical for screening. Saline microbubble contrast-enhanced echocardiography can characterise and monitor RTLIAS, while analysis of interatrial septum motion can predict transatrial pressure gradients and PCWPs (figures 3 and 4; videos 1 and 2).<sup>12 13</sup>

Acute RTLIAS can cause profound hypoxia refractory to oxygen therapy, POS and paradoxical embolism. The pathogenesis of RTLIAS is complex and requires<sup>14–16</sup>:

- 1. An anatomical component (eg, interatrial defect).
- 2. A functional component that transiently increases RA pressures or preferentially directs blood flow through the anatomical component.

With a prevalence of 20%–30% in the general population, PFO is the most common interatrial defect.<sup>14–16</sup> A patient with an asymptomatic interatrial defect may develop RTLIAS with a secondary cardiac or pulmonary insult. Several complications of

COVID-19 can induce or exacerbate pulmonary hypertension and could therefore precipitate RTLIAS. Thus, acute RTLIAS could occur in millions of people with COVID-19 worldwide. However, few reports describe the clinical course of COVID-19 in patients with a PFO.<sup>6–8</sup> Indeed, the contribution of PFO, RTLIAS and POS to hypoxia is often unrecognised.<sup>9 15 16</sup> In a prospective study of 108 mechanically ventilated patients, the overall prevalence of PFO with acute RTLIAS was 27%,<sup>17</sup> but was significantly higher in patients with PEEP over 9 cmH<sub>2</sub>O (45%) or plateau pressure over 26 cmH<sub>2</sub>O (46%).<sup>17</sup> Patients with RTLIAS are ventilated longer, receive more adjuncts to treat refractory hypoxia and have longer admissions in intensive care units.<sup>7–9 16</sup>

However, no data from randomised controlled clinical trials are available to guide the management of RTLIAS.<sup>7 8 16</sup> Indeed, in some situations, the standard approach to the management of refractory hypoxia, which aims to reduce IPS, can exacerbate RTLIAS and may worsen hypoxia.<sup>7 8 16 17</sup> Pragmatic, physiologyguided treatment of hypoxia in patients with RTLIAS should aim to reduce total shunt by balancing the effects of any interventions on both IPS and RTLIAS. Using serial echocardiography to monitor the effect of interventions on RTLIAS could support decision-making in this context as refractory hypoxia with persistent RTLIAS may necessitate closure of the PFO.

Regardless, it is probably best to avoid positive pressure ventilation, initially; if possible, administer oxygen and optimise positioning. If invasive mechanical ventilation is required, supplemental oxygen, plateau pressure and PEEP should be frequently titrated against  $\text{SpO}_2$ , arterial blood gases and haemodynamics so that the lowest airway pressures can be applied. This may be facilitated by measures to improve respiratory system compliance (eg, neuromuscular blockade and prone positioning).<sup>10</sup>

Fundamentally, definitive treatment of RTLIAS requires closure of the anatomical substrate. This may be achieved surgically or percutaneously.<sup>14 15</sup> Treatment of chronic hypoxia and platypnoea–orthodeoxia is a well-recognised indication for PFO closure.<sup>14 18 19</sup> When failure to wean invasive ventilatory support is due to RTLIAS, PFO closure may facilitate liberation from mechanical ventilation.<sup>20</sup> However, secondary prevention of recurrent stroke after a PFO-related stroke is the only indication, currently supported by high-quality data from randomised trials.<sup>21</sup> Further studies are required to define the criteria for closure of PFO in the context of acute respiratory failure.

In select patients, closure of the substrate for RTLIAS could markedly improve hypoxia, reducing the need for

## Learning points

- Consider saline microbubble contrast-enhanced echocardiography to screen for interatrial shunt in patients with severe or refractory hypoxaemia.
- Early diagnosis of right-to-left interatrial shunt may avoid unnecessary mechanical ventilation.
- Avoid interventions that may precipitate or exacerbate rightto-left shunt in patients with an anatomical substrate for interatrial shunt.
- Interatrial shunt can be detected, characterised and monitored using saline microbubble contrast-enhanced echocardiography.
- Acute right-to-left interatrial shunt may resolve as the precipitant (ie, COVID-19) improves, so closure of a patent foramen ovale is not always required.

invasive ventilation and the incidence of paradoxical embolisation. However, while successful closure of the interatrial defect is often reported,<sup>14–16</sup> acute cor pulmonale can develop if pulmonary hypertension is worsened by closing the RTL shunt.<sup>14–16</sup> Furthermore, RTLIAS may improve as the functional trigger resolves, so closure is not always required.<sup>16</sup>

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