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Letter to the Editors-in-Chief

# Systemic thromboemboli in patients with Covid-19 may result from paradoxical embolization

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ABSTRACT

There is increasing evidence that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection causes an unusual pneumonia and a pro-coagulant state that significantly increases the risk of arterial and venous thromboembolism. We hypothesize that, in select patients, some complications of COVID-19 may be due to right-to-left (RTL) shunt. Shunt may be intra-pulmonary, or extra-pulmonary, and can cause paradoxical embolization, hypoxia and platypnoea orthodeoxia. Saline microbubble contrast echocardiography is a minimally invasive, inexpensive, bedside test that can detect, quantify, and define the anatomical substrate of intra-pulmonary and intra-cardiac shunts. The prevalence of patent foramen ovale (PFO) in the general population is high (20–30%) but is even higher in patients who have a stroke (50%). Thus, the striking absence of data on patients with PFO who develop COVID-19 suggests that this is being under-diagnosed. This may be because physicians and sonographers currently feel that screening for shunt is unnecessary. This could be an unintended consequence of guidance from several specialist societies to defer procedures to close PFO until after the pandemic. This may be counterproductive. Patients with shunt may be at particularly high risk of complications from COVID-19 and interventions to minimise RTL shunt could prevent paradoxical embolization and improve hypoxia in select high risk patients with COVID-19.

*Editor,*

The studies describing the incidence of thrombotic complications in patients with Coronavirus Disease 2019 (COVID-19) [1,2] and the scoping review of the thrombosis risk associated with COVID-19 by Al-Ani and colleagues [3] are of great interest. They report that the incidence of venous thromboembolism in patients with COVID-19 is very high [1–3]. Whilst arterial thromboemboli (stroke, myocardial infarction and other systemic emboli) are thought to be less common [1–3], silent cerebral infarcts were revealed in 3 patients when magnetic resonance imaging (MRI) was performed in 13 encephalopathic patients with COVID-19 [4]. So, the true incidence of stroke in COVID-19 is probably under appreciated.

Furthermore, in a series of 32 patients with stroke and COVID-19, cryptogenic stroke (65.6%) was more common than in contemporary controls (30.4%) [5]. This may reflect incomplete assessment. However, data on the risk factors for cryptogenic stroke in COVID-19 are limited. So, atypical or novel mechanisms could cause stroke in patients infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [3]. In this context, it is important to note that, in Yaghi and colleagues' series of 32 patients, cryptogenic stroke was associated with a trend towards higher D-dimer (median 4.8 μg/ml versus 2.1 μg/ml, $p = 0.109$) [5].

These observations contribute to the increasing evidence that SARS-CoV-2 infection causes a pro-coagulant state that significantly increases the risk of thromboembolism. Whilst any infection may induce a pro-coagulant state, the risks of microvascular thrombosis and thromboembolism are particularly high in patients with pulmonary infections [6]. Indeed, the histopathological features of COVID-19 pneumonia include diffuse alveolar damage (i.e. interstitial pneumonia) with widespread thrombotic microvascular involvement [7].

It has previously been suggested that a pro-coagulant state could cause small, 'silent' pulmonary emboli that result in interstitial pneumonia, interstitial lung disease, and progressive lung fibrosis [8]. This process could be relevant in the pathogenesis of interstitial pneumonia in COVID-19.

Pulmonary microvascular thrombosis should increase dead space. However, some patients have more right-to-left (RTL) shunt than expected for the degree of injury apparent on imaging of the lungs [9–11]. The mean RTL shunt fraction of a series of patients with Covid-19 described by Gattinoni and colleagues was 0.50 ± 0.11 despite relatively preserved pulmonary compliance (50.2 ± 14.3 ml/cmH2O) [11]. We hypothesize that the development of RTL shunt in select patients with COVID-19 may contribute to the increased the risk of systemic thromboembolism [9,10]. Al-Ani and colleagues [3] comprehensively reviewed the existing literature for potential pathogenic mechanisms which could account for the increased risk of thromboembolism in patients with COVID-19.

However, discussion of paradoxical embolization, a well-recognised cause of stroke and systemic embolization [9,10,12], was conspicuously absent from their scoping review. We therefore suspect that this phenomenon is being overlooked during the current pandemic.

Patients with COVID-19 pneumonia will almost certainly have some intra-pulmonary shunt [10–12]. Previous studies have reported that the prevalence of intra-pulmonary shunt is higher in patients with cryptogenic stroke (22%) than in matched controls (10%) [13]. This suggests

*Abbreviations:* ARTLIAS, acute right-to-left inter-atrial shunt; COVID-19, Coronavirus Disease 2019; PFO, patent foramen ovale; RTL, right-to-left; SARS CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2

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that intra-pulmonary shunt could facilitate ischaemic cerebrovascular events [13].

As the anatomical substrate for shunt may be intra-pulmonary or extra-pulmonary [9,10]; extra-pulmonary shunt may also be present in select patients with COVID-19 [9,10]. Inter-atrial defects are the most common anatomical substrates for extra-pulmonary shunt. The most common inter-atrial defect is patent foramen ovale (PFO). The prevalence of PFO is significantly higher in patients with a history of ischaemic stroke (prevalence 50%) [12] than in the general population (prevalence 20–30%) [12]. Indeed, prevention of recurrence after a PFO-related stroke is currently the only indication for PFO closure that is supported by randomised controlled trials [10,12].

Although usually asymptomatic, acute RTL inter-atrial shunt (ARTLIAS) can be triggered in patients with inter-atrial defects by any insult that increases right atrial pressure [9,10]. Complications of ARTLIAS include paradoxical embolization, hypoxia and platypnoea orthodeoxia [9,10]. Thus, the increased RTL shunt [11] and the atypical features of COVID-19 respiratory involvement could also be explained by ARTLIAS in some patients [9,10]. Some of the excess mortality and morbidity in patients with a history of stroke who subsequently develop COVID-19 [14] may also be attributable to ARTLIAS in select cases.

Surprisingly, data describing the outcomes of patients with inter-atrial defects who develop COVID-19 are almost non-existent [11]. The peer-reviewed literature includes only one case report describing the clinical course of patient with a PFO who developed COVID-19 and thromboembolic phenomena [15]. An obese 45-year-old woman, treated with ramipril for hypertension, developed pulmonary embolism and a floating atrial thrombus in situ across a PFO [15]. Sadly, despite undergoing embolectomy and receiving extracorporeal membrane oxygenation, this patient died from multiorgan failure [15]. The notable absence of literature describing the interaction between inter-atrial defects and COVID-19 suggests that these congenital cardiac malformations are being underdiagnosed [10].

This is suboptimal because studies performed long before the COVID-19 pandemic demonstrated that critically ill patients with ARTLIAS have worse outcomes [16,17]. They respond poorly to positive end expiratory pressure, are ventilated longer, receive more adjuncts to treat refractory hypoxia, and have longer admissions in ICU [16,17]. There are few data to guide management of patients with extrapulmonary shunt. However, the standard approach to refractory hypoxia may exacerbate ARTLIAS whilst trying to reduce intrapulmonary shunt [16,17]. So management should be guided by the pathophysiology of shunt and should aim to reduce both intra- and extrapulmonary shunt.

Furthermore, consideration of the influence of shunt on the risk of systemic thromboembolism and the severity of COVID-19 are particularly relevant in the context of the 'pressing issues' identified by Al-Ani and colleagues [3]; including the need for scoring systems to stratify patients' risk of developing severe COVID-19 and thrombotic complications [3].

It would therefore be of great interest to determine the incidence of RTL shunt in the series of patients described by Lodigiani et al., 2020 [1] and Klok et al., 2020 [2]. The current understanding of the pathogenesis of COVID-19 would be significantly advanced by subgroup analyses of:

1. Patients without any demonstrable shunt
2. Patients with intra-pulmonary shunt alone
3. Patients with intra-pulmonary and extra-pulmonary shunt

Ideally these subgroup analyses should correlate blood gases, lung mechanics, thromboembolism and outcomes of COVID-19 with the severity of shunt. Intra-pulmonary and intra-cardiac shunt can be detected, quantified and distinguished with saline microbubble contrast echocardiography. This is an inexpensive, minimally invasive bedside test that can be performed during a standard echocardiographic examination.

Although patients with COVID-19 frequently require echocardiography; physicians and sonographers may feel that screening for shunt is currently unnecessary [10]. This is because several specialist societies have recommended that PFO closure should be deferred during the pandemic [6]. This may be counterproductive. Despite the absence of specific data in patients with COVID-19; prevention of recurrence of PFO-related stroke and treatment of hypoxia due to RTL inter-atrial shunt are well recognised indications for PFO closure [10,12]. Patients with shunt may be at high risk of complications from COVID-19 [9,10].

Therefore, if a patient with COVID-19 is having echocardiography anyway, adding a microbubble contrast study could yield significant, clinically relevant information for almost no extra cost. In the absence of another specific indication for echocardiography, we recommend performance of microbubble contrast echocardiography to screen for RTL shunt in patients with COVID-19 if any of the following features are present:

1. Acute symptomatic systemic thromboembolism occurs
2. Silent infarcts revealed by imaging
3. The degree of lung injury identified does not fully account for hypoxia
4. $PaO_2/FiO_2$ ratio over 200 (estimated shunt fraction over 0.2)
5. Supplemental oxygen does not improve hypoxaemia significantly
6. There is a sudden drop in the $PaO_2/FiO_2$ ratio
7. Platypnoea orthodeoxia is present

In patients with COVID-19 the presence of shunt will influence respiratory management [9,10] and may reduce the threshold for treatment with anticoagulation. Furthermore, elimination of the anatomical substrate for the shunt, if possible, by closure of an atrial septal defect or PFO, for example, could prevent paradoxical embolization and improve hypoxia in select high risk patients with COVID-19 [9,10]. Whilst further studies are required to support this PFO closure in this context, we suggest that it is important to screen for RTL shunt in patients with COVID-19 [9,10].

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## CRediT authorship contribution statement

RR developed the hypothesis. All authors were involved in literature search and refinement of the hypothesis. RR prepared the initial draft of the manuscript. All authors were involved with revision of the manuscript and approved the final version of the manuscript for publication.

## Declaration of competing interest

None.

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