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Use of sildenafil in patients with severe COVID-19 pneumonitis

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Patients with SARS-CoV-2 infection develop pulmonary vascular dysfunction with immunothrombosis, endothelitis, pulmonary embolism, and neoangiogenesis of larger vessels.1-3 These changes contribute to dead-space and shunt, increased pulmonary vascular resistance, and right ventricular (RV) dysfunction, and can be improved by therapies modulating endothelial function. Of these, inhaled nitric oxide (NO)5 has pulmonary vasodilating, anti-inflammatory, and potential antiviral properties.5 The phosphodiesterase type 5 inhibitor sildenafil increases endogenous NO, is well tolerated in patients with lung fibrosis,6 but may worsen shunt in acute respiratory
distress syndrome (ARDS). We hypothesised that in patients with COVID-19 ARDS with pulmonary hypertension, RV dysfunction, or both, sildenafil would improve gas exchange. Sildenafil-treated patients with COVID-19 pneumonitis and moderate to severe ARDS were studied between March 1, 2020 and May 31, 2020. The study had ethical approval (A-CLUE 285452, IRAS reference 285452). Oxygenation and carbon dioxide (CO2) clearance were assessed immediately prior, 24 h, 48 h, and 5 days after sildenafil by averaging three blood gas samples and ventilator parameters to calculate the P:F ratio (Pao2/Fio2), oxygenation index, dead space fraction, and ventilatory ratio. Vasoactive drug dose was calculated using norepinephrine equivalents (NE) and the vasoactive-inotropic score (VIS). Initial sildenafil at 12.5 mg three times a day (TDS) was titrated up to 25 mg TDS if tolerated. Patients underwent baseline and follow-up CT scanning (some with dual energy CT pulmonary angiogram [DECTPA], Supplementary material) and detailed echocardiographic assessment (e.g. pulmonary vascular resistance) using the velocity time integral of the pulsed wave Doppler at the RV outflow tract (Supplementary material).

Twenty-five patients (73% male) were included, mean age 54.1 (standard deviation 9) yr; 10 were on veno-venous extracorporeal membrane oxygenation (VV-ECMO), and 11 were proned (Table 1). Baseline echocardiography suggested pulmonary hypertension, RV dysfunction, or both in all patients. Sildenafil was introduced at 6.4 (3.2) days of inhaled NO therapy in some patients to aid weaning of NO (n=15). Sildenafil was administered orally via nasogastric tube at 12.5 mg TDS (n=14) or 25 mg TDS (n=8), or i.v. (10 mg TDS [n=2] or 1 mg h⁻¹ infusion [n=1]) depending on clinician choice and absorption issues. One patient was weaned off sildenafil before ICU discharge; 23 patients continued sildenafil for 12.7 (range 1–60) days at 25 mg TDS.

| Complications, n (%) | AKI requiring CRRT | Superinfection |
|---------------------|-------------------|--------------|
| Died in ICU         | 10 (40)           | 6 (40)       |
| Alive               | 12 (48)           | 9 (60)       |
| Repatriated, outcome unknown | 3 (12)          | 0            |

Table 1: Patient characteristics, haemodynamics, and outcomes. AKI requiring CRRT, acute kidney injury requiring veno-venous haemofiltration; ECMO, veno-venous extracorporeal membrane oxygenation; IQR, inter-quartile range; NE, norepinephrine; P:F, Pao2/Fio2 ratio; sD, standard deviation. A 24 h value significantly different to baseline value at P<0.05 (two-tailed paired t-test).
scan showed reduced PA volume and right atrial area (Table 1). In patients with paired follow-up DECT imaging (n=13), pulmonary iodine density (2.23 [0.59] to 2.86 [0.63] mg ml\(^{-1}\), \(P=0.018\), and % pulmonary perfusion (62.7 [16.8] to 82.7 [17.4], \(P=0.003\) increased.

Brain natriuretic peptide (BNP) (n=19) and hs-troponin (n=25) both decreased, from 84 (28.5–268.0) to 46 (27.3–156) ng L\(^{-1}\), \(P<0.05\) and 18.2 (10.3–62.8) to 12.6 (8.1–31.6) ng ml\(^{-1}\), \(P<0.01\), respectively, from before sildenafil to a 1–2 day time point (troponin) or 1–7 day time point (BNP).

Echocardiography showed baseline tricuspid valve regurgitant (TR) velocity of 3.1 (2.80–3.38) m s\(^{-1}\), RV systolic pressure 39.2 (31.8–45.5) mm Hg, pulmonary valve acceleration time 95 (78.3–115.8) ms, fractional area change (FAC) 38% (29–45%), and tricuspid annular plane systolic excursion (TAPSE) 20.7 (16.7–25.3) mm. On follow-up at 3.8 (2.2) days after sildenafil, pulmonary vascular resistance (n=9) decreased from 2.35 (1.89–3.05) to 2.02 (1.57–2.58) Wood units (\(P=0.03\), and LV cardiac output (n=13) increased from 5.73 (4.60–7.03) to 7.13 (5.88–7.79) L min\(^{-1}\) (\(P=0.006\)) (Supplementary Table S1).

Nine patients died in ICU (four ECMO recipients), a 36% 90-day mortality. Of the survivors, median (range) ICU length of stay was 39 (14–85) days. At last follow-up, 324 (28–463) days after hospital discharge, 12/13 patients had normal echocardiography (one had persistent pulmonary hypertension) with fraction of expired volume at 1 s (FEV\(_1\)) 2.08 (1.89–3.09), 94% (80–103%) of predicted, forced vital capacity (FVC) 2.5 (2.13–3.77) L, 86% (75–95%) of predicted, FEV\(_1\)/FVC 0.82 (0.79–0.87), transfer capacity (TLCO) 57% (43.5–74%) of predicted, and KCO 89% (72.2–97%) of predicted, four had mild parenchymal changes, and one had a persistent perfusion defect on follow-up CT (n=12).

We report outcomes with sildenafil in a well characterised cohort of ARDS patients with pulmonary hypertension or RV dysfunction as a result of COVID-19. Although a single sildenafil dose can cause hypotension and deterioration in oxygenation in ARDS (without associated pulmonary hypertension or RV dysfunction), this study suggests sildenafil was well tolerated in COVID-19 ARDS, without deterioration in oxygenation, dead space, or haemodynamics, and improved cardiac biomarkers and echocardiographic features.

Several factors further to dosing may explain the potential beneficial effects in this cohort. Pulmonary vascular and RV dysfunction are common in COVID-19 ARDS. Increased cardiac output as a result of reduced pulmonary vascular resistance and improved RV function, as supported by improvement in cardiac biomarkers, may have augmented oxygen delivery. Gas exchange did not deteriorate with sildenafil, suggesting that intrapulmonary shunt or potential ventilation-perfusion mismatch was balanced by beneficial effects (e.g. on cardiac output). The potential for improvement in longer term lung function impairment remains to be seen.

This report is of course limited by its retrospective and non-randomised nature. Despite limitations, our results suggest that sildenafil is safe in carefully selected COVID-19 ARDS patients. Supporting these observations, a recent randomised trial of sildenafil reported reduced hospital stay and need for mechanical ventilation in ward patients with COVID-19 and perfusion deficits on DECTPA (not selected for RV dysfunction). These developments are encouraging given that a pulmonary vasculopathy appears central to the pathophysiology of severe acute COVID-19, and sildenafil therapy merits further exploration in randomised trials.

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**Declarations of interest**

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.04.004.

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Correspondence—We commend Fischer and colleagues1 for investigating this novel approach of using central venous oxygen saturation (ScvO2) to determine red blood cell (RBC) transfusion triggers for cardiac surgical patients. Maximising tissue oxygenation whilst minimising the risks of blood transfusion are both laudable aims of perioperative care.

We are compelled to raise several points. Firstly, we would advise caution with the conclusion of the paper that such an approach is safe in terms of postoperative morbidity and mortality, given the lack of power to identify these secondary outcomes. The authors have appropriately powered their study to demonstrate that using ScvO2 to guide RBC transfusion resulted in a more restrictive transfusion strategy. This may be a worthy aim, but it is a process outcome, primarily useful in establishing the feasibility for future large-scale trials.2 Whilst the authors allude to this in their initial rationale and part explain why three international studies, ProMISE, ARISE, and ProCESS, did not replicate the results of Rivers and colleagues3 to which the authors refer in their initial rationale for using this measure.3–6

Lastly, we wonder whether clinically relevant endpoints can be extrapolated in this cohort of patients without reporting the volume of RBCs transfused on the ICU or an understanding of what was administered intraoperatively and after discharge to lower acuity wards. With specific regard to this study, it is interesting to note that whereas group separation may well have initially taken place in terms of delivering a restrictive transfusion regime, mean haemoglobin values in both cohorts remained between 9.0 and 9.6 g dl–1 on Days 1, 2, and 7. Given that the risks associated with transfusion are largely summative and that increased volume transfused may also represent surgical complexity and the preoperative haemoglobin and volume status of the patient, future studies reporting long-term clinical outcomes should likely examine patient blood management throughout the entirety of their perioperative course.

Declarations of interest
The authors declare that they have no conflicts of interest.

Individualised or liberal red blood cell transfusion after cardiac surgery. Comment on Br J Anaesth 2021; 128: 37–44

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