Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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doi: 10.1016/j.bja.2022.04.003
Advance Access Publication Date: 15 April 2022

Use of sildenafil in patients with severe COVID-19 pneumonitis

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Keywords: acute respiratory distress syndrome; COVID-19; extracorporeal membrane oxygenation; pulmonary hypertension; right ventricular failure; sildenafil

Editor—Patients with SARS-CoV-2 infection develop pulmonary vascular dysfunction with immunothrombosis, endotheliitis, 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,[4] 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.[6] The phosphodiesterase type 5 inhibitor sildenafil increases endogenous NO, is well tolerated in patients with lung fibrosis,[7,8] but may worsen shunt in acute respiratory

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, Pa_{O_2}:Fi_{O_2} ratio; SD, standard deviation. *A 24 h value significantly different to baseline value at $P<0.05$ (two-tailed paired *t*-test).

	All *n*=25	Non-ECMO *n*=15	ECMO *n*=10
Age, yr	54 (38–61.5)	60 (54–63.5)	49 (43.8–49)
Sex, male, *n* (%)	19 (73)	9 (60)	10 (91)
BMI, kg m^{-2}	29.6 (6.1)	29.2 (6.7)	30.1 (5.5)
Comorbidities, n (%)			
Systemic hypertension	13 (50)	10 (67)	3 (27)
Diabetes mellitus	8 (31)	6 (40)	2 (18)
Asthma	3 (12)	2 (13)	1 (9)
Smoking	11 (42)	9 (60)	2 (18)
Complications, n (%)			
AKI requiring CRRT	12 (46)	9 (60)	3 (27)
Superinfection	15 (58)	10 (67)	5 (45)
Days on sildenafil (median, IQR)	7.5 (3.9–14.6)	7 (3–20.7)	7.9 (4.7–12.8)
Max daily dose (mean [SD] oral equivalent mg)	66.4 (18.5)	65.0 (21.0)	68.2 (15.2)
Ventilatory parameters			
P:F ratio baseline, kPa	19.8 (6.2)	17.7 (5.9)	22.9 (5.8)
P:F ratio at 24 h, kPa	24.1 (7.3)*	20.9 (6.0)*	28.6 (7.3)*
Dead space ratio baseline	0.29 (0.16)	0.26 (0.11)	0.33 (0.21)
Dead space ratio 24 h	0.30 (0.16)	0.26 (0.09)	0.35 (0.23)
Ventilatory ratio baseline	n/a	2.6 (0.3)	n/a
Ventilatory ratio 24 h	n/a	2.5 (0.5)	n/a
Haemodynamics			
Norepinephrine equivalents pre, μg kg^{-1} min^{-1}	0.08 (0.06)	0.09 (0.07)	0.06 (0.04)
Norepinephrine equivalents 24 h, μg kg^{-1} min^{-1}	0.12 (0.15)	0.14 (0.19)	0.09 (0.06)*
Vasoactive-inotropic score baseline	7.9 (5.9)	9.3 (6.9)	6.1 (3.8)
Vasoactive-inotropic score 24 h	11.8 (13.7)	13.7 (17.3)	9.4 (6.2)*
MAP baseline, mm Hg	74.9 (5.8)	73.9 (5.0)	76.2 (6.7)
MAP 24 h, mm Hg	74.7 (5.1)	74.8 (5.4)	74.7 (4.9)
HR baseline, beats min^{-1}	82.8 (15.4)	87.0 (14.0)	77.1 (16.0)
HR 24 h, beats min^{-1}	86.9 (17.6)	90.2 (17.6)	82.5 (17.5)
Outcome (as of Nov 2020), n (%)			
Alive	12 (48)	9 (60)	3 (30)
Died in ICU	10 (40)	6 (40)	4 (40)
Repatriated, outcome unknown	3 (12)	0	3 (30)

distress syndrome (ARDS).[9] 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 (CO_2) clearance were assessed immediately prior, 24 h, 48 h, and 5 days after sildenafil by averaging three blood gas and ventilator parameters to calculate the P:F ratio (Pa_{O_2}:Fi_{O_2}), oxygenation index,[10] dead space fraction,[11] and ventilatory ratio.[12] Vasoactive drug dose was calculated using norepinephrine equivalents (NE)[13] and the vasoactive-inotropic score (VIS).[14] 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.

NE and VIS increased 24 h after initiation of sildenafil therapy (Table 1). Norepinephrine doses increased in 14, decreased in 10, and remained unchanged in 1 patient. MAP (74.9 [5.8] to 74.7 [5.1] mm Hg, $P=0.9$) and HR (82.8 [15.4] to 86.9 [17.6] bpm $P=0.09$) were stable 24 h after sildenafil. ECMO patients were on lower initial doses but had significant increases after sildenafil initiation (0.06 [0.04] to 0.09 [0.06] μg kg^{-1} min^{-1}; $P=0.02$). There was no haemodynamic instability as a direct result of sildenafil that necessitated treatment discontinuation.

The P:F ratio increased in non-ECMO patients from 17.7 (5.9) to 20.9 (6.0) kPa ($P<0.01$) (Table 1 and Supplementary Fig. S1) 24 h after sildenafil. Dead-space and ventilatory ratios were unchanged at 24 h in non-ECMO patients (0.26 [0.11] to 0.26 [0.09]) and (2.6 [0.3] to 2.5 [0.4]; $P=0.25$), respectively, and dead-space fraction was static in ECMO patients (0.33 [0.22] to 0.35 [0.23]).

Baseline CT scans showed pulmonary embolism in 17 (68%) patients, pulmonary artery (PA) volume 75.4 (18.3) ml, PA diameter 32.6 (2.7) mm, and right atrial area 16.2 (4.4) mm^2. Follow-up CT scans (*n*=21) 12 (6.25–15) days after the initial

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, FEV1/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[15] 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).[16] 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.

Funding

CM is supported by a grant from the National Institute for Health and Care Research, award number 156882.

Declarations of interest

CM declares personal fees from Edwards Lifesciences. BP declares personal fees from GSK and grants from Mermaid Care A/C, ESICM, RBHT charity, European Commission, Academy of Medical Sciences and Imperial College London Covid fund. SJW declares grants and personal fees from Actelion and Bayer and personal fees from GSK and MSD. LP declares personal fees from Actelion. The other authors declare no conflict of interest with regard to the production or submission of this manuscript.

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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doi: 10.1016/j.bja.2022.04.004
Advance Access Publication Date: 15 April 2022

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

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Keywords: cardiac surgery; central venous oxygen saturation; patient blood management; red blood cell transfusion; outcomes

Editor—We commend Fischer and colleagues[1] for investigating this novel approach of using central venous oxygen saturation ($ScvO_2$) 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 paper, they also claim that a clinically relevant outcome has been found (i.e. that such a strategy is non-inferior to a more liberal one). Without initially powering the study to examine differences in morbidity and mortality, reporting that it is safe in this respect may result in clinicians inappropriately deploying this approach believing this to be a seemingly definitive assessment of the subject.

We also question the overall utility of $ScvO_2$ to guide RBC transfusion when the authors report no significant increase in $ScvO_2$ after administration of RBC transfusion. In principle, $ScvO_2$ provides a good composite reflection of the systemic oxygen uptake to oxygen delivery ratio. However, a more complex system contributing to tissue oxygenation may well occur, especially in inflammatory states such as sepsis and after exposure to a cardiopulmonary bypass circuit. This could partly explain why three international studies, ProMISE, ARISE, and ProCESS, did not replicate the results of Rivers and colleagues[3] 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.

DOI of original article: 10.1016/j.bja.2021.09.037.