Severe Acute Cor Pulmonale in Patients with COVID-19 Acute Respiratory Distress Syndrome: Caution with Left Turn

To the Editor:

Moderate to severe acute respiratory distress syndrome (ARDS) is associated with acute cor pulmonale (ACP) in 22% of patients under protective ventilation (1). When severe, ACP appears prognostic (1). Patients with coronavirus disease (COVID-19) ARDS frequently require prone positioning (PP) due to profound hypoxemia (2). PP requires a transition from the supine to the lateral position. Hemodynamic effects of changes in body position have been scarcely studied (3). We herein report two cases of cardiac arrest occurring in the left lateral position during the transition from the supine to PP in patients ventilated for severe COVID-19 ARDS associated with severe ACP. We also monitored the effect of body positioning on the ventricular interaction in two additional patients ventilated for COVID-19 ARDS with different severity of right ventricular (RV) involvement, using real-time three-dimensional (RT3D) transesophageal echocardiography (TEE).

Cases

The first patient was a hypertensive 76-year-old man with diabetes who was ventilated 24 hours after ICU admission for severe COVID-19 ARDS. TEE depicted a severe ACP and concentric left ventricular (LV) hypertrophy with a medioventricular obstruction (Table 1). The patient was hemodynamically stable without vasopressor support but remained severely hypoxemic, and prone ventilation was decided. Within the first minute in the left lateral position, the patient rapidly sustained profound hypotension associated with severe bradycardia and subsequent asystole. No drop in arterial saturation was recorded. Immediate cardiopulmonary resuscitation allowed the prompt return of spontaneous circulation. A second TEE examination ruled out a proximal pulmonary embolism. The patient subsequently developed intractable shock.

The second patient was a 52-year-old woman without past medical history who was ventilated 48 hours after ICU admission for severe COVID-19 ARDS. TEE disclosed a nonsymptomatic severe ACP without proximal pulmonary embolism (Table 1). Both severe hypoxemia and ACP prompted PP. The patient was left in the left lateral position for 3 min for nursing purposes before being installed prone. During this period, the patient progressively collapsed without oxygen desaturation and sustained pulseless activity. Immediate cardiopulmonary resuscitation was unsuccessful.

Two additional patients ventilated for severe COVID-19 ARDS with symmetrical lung lesions and different degrees of RV involvement were monitored using RT3D TEE to depict the effects of body positioning on ventricular interaction (Table 1). None received inhaled nitric oxide or vasopressor support. Driving pressure increased in the lateral position, especially in the left position in the patient with ACP (Table 1). The transition from supine 45° to lateral position resulted in an increase of RV/LV volume ratio, the difference being more marked at end-diastole, in the left than in the right lateral position, and in the patient with severe ACP than with isolated RV dilatation (+41% and +19% vs. +35% and +12%, respectively). This is presumably related to a more deleterious hemodynamic effect of body positioning in the presence of ACP, which is characterized by the acute dilatation of the RV at the expense of the LV since the sum of end-diastolic volumes cannot increase abruptly in the stiff pericardial sac (4), and to the further LV restriction at end-systole due to the leftward shift of the interventricular septum secondary to prolonged RV contraction aimed at compensating its increased afterload (4, 5). A similar trend was observed with RV longitudinal free wall strain denoting systolic impairment (Table 1). Finally, in the left lateral position, the enlarged RV is anatomically located above the LV. Overall, these postural changes tend to further increase LV restriction by a transient worsening of RV dilatation and paradoxical septal motion during the transition from the 45° supine to the left lateral position and potential direct LV compression (Figure 1).

Discussion

Hemodynamic effects of lateral positioning have been poorly studied and never evaluated in patients ventilated for ARDS with severe ACP (3). The mechanisms underlying worsened RV impairment in the left lateral position remain unclear. Lung mechanics appeared more altered in the left lateral than in the right lateral position in our two patients, as reflected by increased driving pressure and decreased static compliance (Table 1). Riad and colleagues (6) showed that lung resistance as well as lung and chest wall elastance increase immediately in the lateral position. In addition, in healthy anesthetized dogs and pigs, RV systolic and end-diastolic pressure significantly increase from the supine to the lateral position and even more in the left than right lateral position (7). The good hemodynamic tolerance of the left lateral position in our patient with severe ACP may be ascribed to *1*) the absence of LV hypertrophy and associated vasoplegia, which may exacerbate the negative effect of LV unloading during the change in body position (as opposed to case #1), and *2*) the shortened duration of the transition in the left lateral position under careful TEE monitoring (as opposed to case #2). In other clinical settings, left lateral positioning appears safe even when performed for a longer period (8). It may be required in specific circumstances in patients with severe ARDS (e.g., extracorporeal membrane oxygenation cannula).

Changes in RV properties and ventricular interaction induced by body positioning have presumably been overlooked in clinical practice since patients usually remain hemodynamically stable, and continuous monitoring has been scarcely reported, especially using RT3D TEE (9). In the PROSEVA study, cardiac arrest has been reported twice as much in the supine than in the prone group (13.5% vs. 6.8%), but in only two patients during prone ventilation (2 of 466: 4‰) (10). In our ICU, prone positioning was performed 190 times in 109 ventilated patients for COVID-19 ARDS over 18 months, with no other fatal complication. Accordingly, cardiac arrest during body positioning appears rare and should not discourage

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Table 1. Main Characteristics of the Two Reported Fatalities and Two Other Ventilated Patients for COVID-19 Acute Respiratory Distress Syndrome with Different Severity of Right Ventricular Involvement for Comparison, and Effects of Changes in Body Position on Right Ventricular Size and Function, and on Ventricular Interaction as Monitored by Real-Time Three-Dimensional Transesophageal Echocardiography*

Characteristics and Parameters	Case #1†: Supine 45°	Case #2 Supine 45°	Severe Acute Cor Pulmonale					Isolated Moderate RV Dilatation				
			Supine 45°	Supine 0°	Right Lateral	Left Lateral	Prone	Supine 45°	Supine 0°	Right Lateral	Left Lateral	Prone
Patient's characteristics												
Age, yr	76	52	40					50				
Contrast-enhanced chest CT scan‡	46% Bilateral, symmetrical lesions (ground-glass opacity and crazy-paving); no pulmonary embolism	45% Bilateral, symmetrical lesions (ground-glass opacity and crazy-paving); no pulmonary embolism	47% Bilateral, symmetrical lesions (ground-glass opacity and crazy-paving); no pulmonary embolism					77% Bilateral, symmetrical lesions (ground-glass opacity and crazy-paving); no pulmonary embolism				
Length of invasive ventilation/ ICU stay before event or hemodynamic assessment, d	7/9	6/9	4/9					10/12				
Inhaled nitric oxide	No	No	No					No				
Vasopressor support	No	No	No					No				
Hemodynamic parameters												
Heart rate, bpm	111	125	129	129	134	134	138	120	103	104	115	118
Systolic/diastolic blood pressure, mm Hg	127/74	119/78	157/95	154/95	127/72	170/108	150/90	153/78	154/78	182/86	141/66	149/81
Ventilatory parameters§												
SpO_2, %	91	92	86	86	85	81	87	90	88	89	88	90
Pa_{O_2}/FI_{O_2}	81	60	60	—	—	—	—	64	—	—	—	—
Pa_{CO_2}, mm Hg	62	72	83	—	—	—	—	110	—	—	—	—
Tidal volume, ml/kg	6.8	6	4.2	4.2	4.2	4.2	4.2	6	6	6	6	6
PEEP, cm H_2O	10	10	7	8	8	9	7	8	8	8	8	8
Plateau pressure, cm H_2O	19	27	29	34	28	36	28	26	24	28	30	26
Driving pressure, cm H_2O	9	17	22	26	20	27	21	18	16	20	22	18
Compliance, ml/cm H_2O	50	24	15	12	16	12	15	22	25	20	18	22
Echocardiography parameters‖												
3D RV end-diastolic volume, ml	96	115	140	147	145	155	138	121	127	122	133	112
3D RV end-systolic volume, ml	47	80	95	97	106	90	85	46	46	47	47	37
3D LV end-diastolic volume, ml	23	41	54	43	47	43	51	109	89	99	89	83
3D LV end-systolic volume, ml	5	20	27	21	24	21	22	35	31	34	34	31
3D RV/LV end-diastolic volume (modification from supine 45°), %	4.17	2.8	2.59	3.46 (+33)	3.07 (+19)	3.65 (+41)	2.72 (+5)	1.11	1.43 (+29)	1.24 (+12)	1.5 (+35)	1.34 (+22)
3D RV/LV end-systolic volume (modification from supine 45°), %	9.4	4.0	3.58	4.6 (+29)	4.5 (+25)	5.1 (+43)	3.9 (+8)	1.31	1.48 (+13)	1.38 (+6)	1.4 (+7)	1.18 (−10)
RV longitudinal free wall strain, %	−29	−15	−21	−17	−18	−13	−22	−27	−24	−25	−24	−28
TAPSE, mm	17	13	19	—	—	—	—	24	—	—	—	—
Tricuspid S′ wave, cm/s	14	—	14	—	—	—	—	17	—	—	—	—

Definition of abbreviations: 3D = three-dimensional; bpm = beats/min; COVID-19 = coronavirus disease; CT = computed tomography; LV = left ventricle; PEEP = positive end-expiratory pressure; RV = right ventricle; TAPSE = tricuspid annulus plane systolic excursion.

*All values were recorded within 30 s after the change of body positioning, using the same time sequence as indicated in the columns from left to right.

†A concentric left ventricular hypertrophy associated with a hyperkinetic left ventricle and medio-ventricular dynamic obstruction was observed.

‡Quantification of lung lesions was obtained using a dedicated software (Advanced Workstation Server–Thoracic V-care application; General Electric).

§No change in ventilator settings during changes in body position.

‖Each echocardiography measurement was performed independently by two distinct operators using QLAB 13 (Philips) and TOMTEC software for the measurement of the right ventricle volume. Results were similar with <5% of interobserver variability. Data shown are the averages of the two measurements.

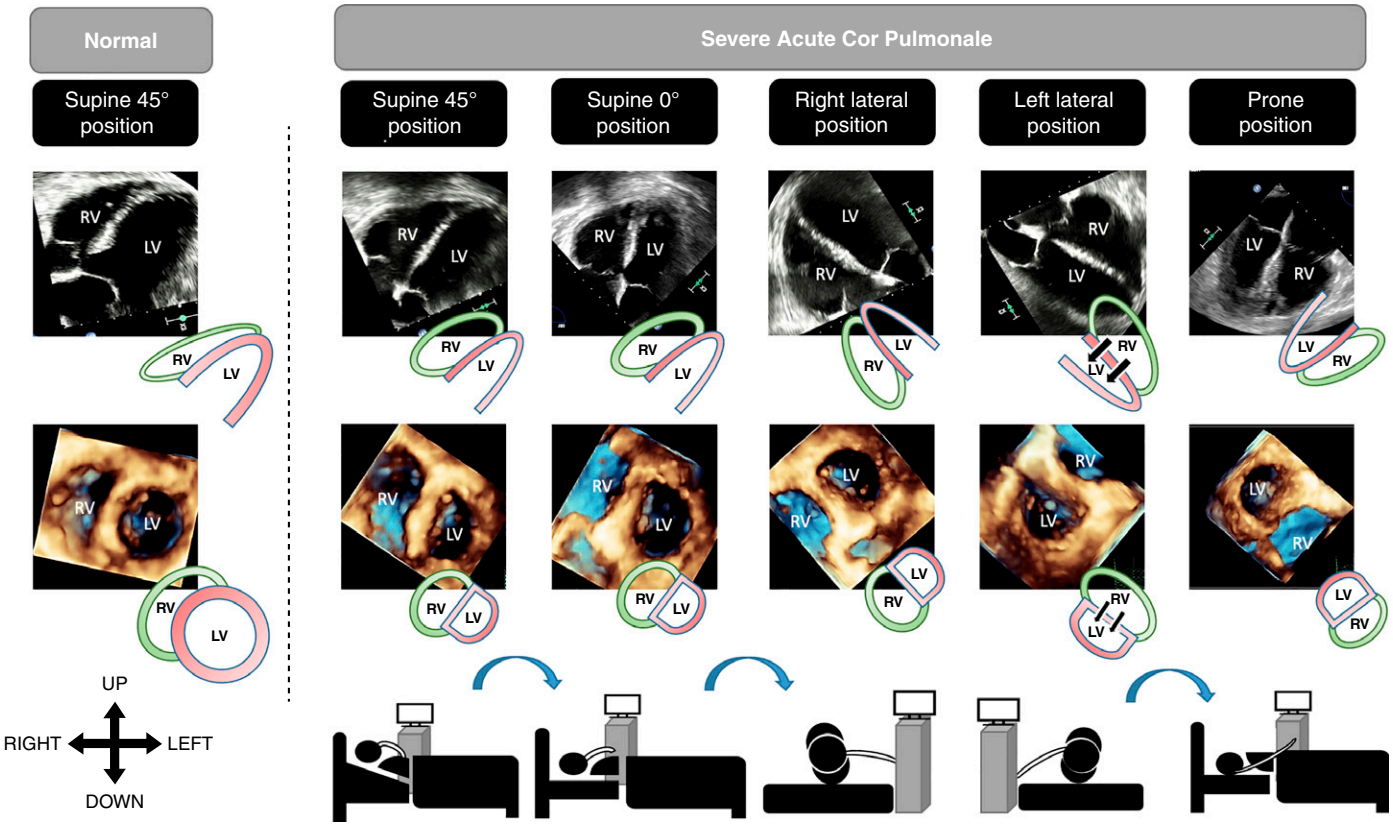

Figure 1. Real-time three-dimensional (RT3D) transesophageal echocardiography was performed in a 40-year-old patient ventilated for severe acute respiratory distress syndrome related to coronavirus disease (COVID-19) with a severe acute cor pulmonale. A normal heart imaged in the supine 45° position is shown for comparison (left panels). The successive changes in body position are displayed at the bottom in the time sequence they have been performed from left to right. Images are oriented following the anatomical position of the heart within the chest when examined from the esophagus in various body positions, using the same representation as a chest computed tomographic scan. In the right lateral position, the right ventricle (RV) is in a dependent position and no significant morphological changes compared with the supine position were evidenced. In contrast, during the left lateral position, the RV is anatomically located above the left ventricle (LV). This results in a further restriction of the LV in the stiff pericardial sac due to *1*) a direct compression by an increased dilatation of the RV as reflected by a higher RV/LV volume ratio, and *2*) an exacerbation of end-systolic bulging of the interventricular septum toward the LV (black arrows). Hemodynamic parameters were kept steady without vasopressor support throughout the changes of body position, whereas respiratory mechanics were most impaired in the left lateral position (*see* Table 1). Each RT3D measurement was performed offline and independently by two experts in echocardiography on two distinct RT3D acquisitions in each body position. Reported values are the mean of these measurements. Written consents were obtained at discharge in survivors.

performing prone ventilation in patients with COVID-19 ARDS when indicated while closely monitoring airway pressures. Larger prospective studies are needed to further describe hemodynamic effects of body positioning, especially in the presence of RV injury and to determine if they are influenced by the severity and cause of ARDS.

We suggest performing echocardiography before PP to search for a severe (even nonsymptomatic) ACP. When present, the transition from supine to PP might preferably use right lateral positioning as an attempt to reduce additional circulatory burden due to transiently worsened deleterious ventricular interaction. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Cyclosporin A Reveals Potent Antiviral Effects in Preclinical Models of SARS-CoV-2 Infection

To the Editor:

Betacoronaviruses readily infect humans and cause pandemic outbreaks once new variants emerge from zoonotic reservoirs, such as severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–2003, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019. Coronavirus disease (COVID-19) is characterized by an early oligosymptomatic phase with high viral replication in the upper respiratory tract that may progress to pneumonia, respiratory failure, and a severe systemic inflammatory response, causing more than 4 million deaths worldwide to date. Despite ongoing vaccination programs, effective and readily available drugs are still needed, considering the high number of those unvaccinated or the rapidly waning immunity in some risk groups, together with novel immune escape variants. Currently available broadly antiinflammatory treatment options such as corticosteroids (1) or additional IL-6R antagonists are applied in severe COVID-19, but for the latter, trial results regarding mortality are conflicting (2, 3). The only SARS-CoV-2 antiviral that has been applied routinely in humans, remdesivir, failed to reduce 28-day mortality in the Solidarity trial and is no longer recommended by the World Health Organization (4).

Combining antiviral and immunomodulatory effects, the immunophilin inhibitor cyclosporin A (CsA) is a promising candidate for the treatment of different CoVs. CsA is a U.S. Food and Drug Administration–approved immunosuppressive drug in medical use since 1983 to prevent graft-versus-host disease after organ transplant. CsA blocks the peptidyl-prolyl *cis-trans* isomerase activity of cyclophilins mediating diverse cellular processes (e.g., protein folding) (5). Protein–protein interaction screens revealed that cyclophilins are direct interaction partners of the SARS-CoV nonstructural protein 1, highlighting cyclophilins as important targets for antivirals. Accordingly, CsA was found to block replication of different viruses, including CoVs, *in vitro* (6). In an attempt to decipher the putative mode of action, we recently revealed that CsA, despite its known immunosuppressive actions in T lymphocytes, elicits a potent antiviral immune response by inducing IFN regulatory factor 1–dependent IFN-lambda (type III IFN) release, resulting in IFN-stimulated gene–dependent antiviral reprogramming of the lung epithelium and preservation of barrier function after MERS-CoV infection *in vitro* and *in vivo* (7). Moreover, a retrospective observational study of patients with COVID-19 treated with CsA demonstrated a significant mortality decrease (8).

Here, we demonstrate that CsA acts as a potent antiviral against different SARS-CoV-2 isolates in translational *in vitro*/*ex vivo* and *in vivo* models. Human bronchial epithelial cells (HBEpCs) of six different donors fully differentiated under air–liquid interface conditions for at least 21 days were infected with SARS-CoV-2 (BavPat1/2020 isolate, European Virus Archive Global 026V-03883, München-1.1/2020/929; termed "wild type" [WT]), resulting in significant replication with viral particle release into the medium of the apical compartment. CsA (10 μM) did not reveal substantial cytotoxicity in this model (not shown) and reduced SARS-CoV-2 *E* gene expression and viral titers significantly compared with control (Figures 1A and 1B). We then used donor lung–derived precision-cut lung slices (PCLSs) that were viable in *ex vivo* culture after sectioning for up to 14 days for infection with SARS-CoV-2 WT and CsA or DMSO treatment. Of note, SARS-CoV-2 replicated efficiently in PCLSs (9). SARS-CoV-2 *E* gene expression was quantified in homogenates together with viral titers in supernatant. Application of CsA significantly reduced virus titers in the medium and *E* gene RNA compared with DMSO-treated control (Figures 1C and 1D);

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