Peculiar hemodynamic characteristics of COVID-19 patients with acute respiratory distress syndrome requiring mechanical ventilation. An invasive assessment using right heart catheterization

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ABSTRACT

Aims. Interstitial pneumonia due to 2019 coronavirus disease (COVID-19) is often complicated by severe respiratory failure. In addition to reduced lung compliance and ventilation/perfusion mismatch, a blunted hypoxic pulmonary vasoconstriction has been hypothesized, that could further promote the intrapulmonary shunt (Qs/Qt) and explain part of the peculiar pathophysiology of the COVID-19 cardio-respiratory syndrome. However, no invasive hemodynamic characterization of COVID-19 patients has been reported so far.

Methods and results. Twenty-one mechanically-ventilated COVID-19 patients underwent right heart catheterization and echocardiography. Their data were compared both with those obtained from non-mechanically-ventilated paired control subjects matched for age, sex and body mass index, and with pooled data of 1937 patients with “typical” acute respiratory distress syndrome (ARDS) from a systematic literature review. Left ventricular mass was higher in COVID-19 patients than in controls ($p<0.01$), despite a similar prevalence of hypertension. Cardiac index was higher in COVID-19 patients than in controls (3.8 [2.7-4.5] vs 2.4 [2.1-2.8] L/min/m^2, $p<0.001$), but slightly lower than in ARDS ($p=0.024$). Qs/Qt and lung compliance were inversely related in COVID-19 ($r=-0.57$, $p=0.011$) and did not differ from ARDS. Despite this, pulmonary vascular resistance of COVID-19 was normal, similar to that of control subjects (1.6 [1.1-2.5] vs 1.6 [0.9-2.0] WU, $p=0.343$), and lower than reported in ARDS ($p<0.01$). Pulmonary hypertension was present in 76% of COVID-19 and in 19% of control subjects ($p<0.001$), and it was always post-capillary. Pulmonary artery wedge pressure was higher in COVID-19 than in ARDS, and inversely related to lung compliance ($r=-0.46$, $p=0.038$).

Conclusions. The hemodynamic profile of COVID-19 patients needing mechanical ventilation is characterized by combined cardio-pulmonary alterations. Low pulmonary vascular resistance, coherent with a blunted hypoxic vasoconstriction is associated with high cardiac output and post-capillary pulmonary hypertension, that could eventually contribute to lung stiffness, and promote a vicious circle between the lung and the heart.

Keywords: hemodynamics, pulmonary hypertension, heart failure, COVID-19, ARDS

The current pandemic due to 2019 novel coronavirus disease (COVID-19) represents an unprecedented and severe public health problem, burdened with high rates of hospitalization and mortality, as in the case of Northern Italy [1-3]. It may cause interstitial pneumonia and, in up to 15% of patients, it progresses towards severe acute respiratory syndrome, frequently complicated

by acute respiratory distress syndrome (ARDS) [4]. ARDS is typically characterized by inflammatory alveolar edema associated with stiff lungs and severe gas exchange impairment, presenting as acute onset of noncardiogenic pulmonary edema and severe hypoxemia [5]. Non-ventilated, poorly compliant lung zones generally represent the anatomical bases for intrapulmonary shunting, which further deteriorates arterial oxygenation. Pulmonary hypertension is a frequent finding, mainly attributed to hypoxic pulmonary vasoconstriction, thromboembolism, and, eventually, vascular remodeling [6].

It has been reported that the ARDS caused by COVID-19 may present some “atypical” features, including a relatively preserved lung compliance and a high intrapulmonary shunt fraction (increased Qs/Qt) [7]. The latter could be a major contributor to the severity of the respiratory failure, and has been speculatively attributed to an abnormally blunted hypoxic pulmonary vasoconstriction [7-9]. Coherently, preliminary data collected with dual energy computed tomography of the chest have shown dilated subsegmental pulmonary arteries proximal to, and within the lung consolidation areas, with increased perfusion, that could represent the anatomical-functional basis of intrapulmonary shunt [8]. However, a thorough hemodynamic characterization in COVID-19 patients with ARDS and needing mechanical ventilation has not been described so far [9].

During the emergency conditions imposed by the COVID-19 outbreak in Northern Italy regions, allocation of resources dramatically changed [2]. Due to the limited amount of beds in general intensive care unit, a number of COVID-19 patients at our centers were randomly admitted in the cardiac surgery intensive care unit beds equipped for invasive hemodynamic monitoring, which is frequently a standard of care for attending physicians. In this context, right heart catheterization was performed on clinical ground on a more frequent basis than it is normally done in the context of non-COVID-19 ARDS, with the hope to acquire potentially useful information for the management of these patients: understanding of COVID-19 manifestations, including cardiovascular involvement [10-13], was unsatisfactory [3], and mortality rate in the intensive care unit was high. We then decided to take advantage of this experience and to report these invasive hemodynamic data, that might be of aid for a better understanding of COVID-19 pathophysiology [9]. Aim of this study was therefore to characterize cardiopulmonary hemodynamics of mechanically-ventilated patients with ARDS due to COVID-19.

METHODS

We retrospectively analyzed data of consecutive patients with ARDS due to laboratory-confirmed COVID-19, admitted to the Intensive Care Unit of Ospedale San Luca (Istituto Auxologico Italiano, Milan), and Ospedale Papa Giovanni XXIII (Bergamo), Italy, between February 25th and April 15th, 2020. We included patients needing mechanical ventilation, and who underwent right heart catheterization.

We excluded from this analysis COVID-19 patients with: incomplete hemodynamic data, pre-existing severe cardiac or respiratory disease, such as reduced left ventricular (LV) ejection fraction, more than mild chronic obstructive pulmonary disease, pulmonary vascular disease, cirrhosis, malignancy and those with acute extensive pulmonary thromboembolic manifestations (i.e. bilateral pulmonary artery peripheral involvement, or obstruction of the left or the right branches of the pulmonary artery), that could relevantly affect hemodynamics. Due to the high prevalence of pulmonary embolism reported in this cohort [15], patients with previous demonstration of small, segmental or subsegmental pulmonary embolism were included, provided that they had been appropriately treated. Indeed, at least 30% of the pulmonary vascular bed should be involved before hemodynamic changes appear [17]. Additionally, it has been previously reported that pulmonary microthrombosis, which could be an issue in mechanically-ventilated ARDS patients, should not relevantly affect hemodynamics [18].

We compared invasive hemodynamics of mechanically-ventilated COVID-19 ARDS with non-ventilated controls, in analogy to pioneering studies that could demonstrate hypoxic pulmonary vasoconstriction as a peculiar characteristic of ARDS, since low pulmonary compliance that characterize ARDS might lead to a negligible transmission of pressure to the pulmonary vascular bed [14,15]. Furthermore, in order to strengthen our results, we also compared cardiorespiratory characteristics of our patients with pooled data obtained from a systematic literature review on hemodynamics in mechanically-ventilated patients with ARDS.

Clinical characteristics of patients, including ventilatory parameters, blood tests and medical treatment at the time of hemodynamic assessment, were retrieved from medical records.

Controls were selected among outpatients who underwent an elective right heart catheterization for unexplained dyspnea after a comprehensive non-invasive evaluation at Ospedale San Luca, Istituto Auxologico Italiano, Milan, between June 2016 and December 2019. A 1:1 matching by age, sex and body mass index (BMI) with COVID-19 patients was performed after having excluded

patients with reduced left LV ejection fraction, more than mild chronic pulmonary obstructive disease, pulmonary vascular disease.

Furthermore, we conducted systematic Medline literature review, updated to August 26th 2020, in order to compare hemodynamic characteristics of our COVID-19 patients with available published data. We used the following combinations of search terms: ("pulmonary vascular resistance" OR "pulmonary hemodynamics" OR "pulmonary haemodynamics" OR "pulmonary circulation" OR "pulmonary vessels" OR "pulmonary vasoconstriction" OR "pulmonary hypertension" OR "intrapulmonary shunt") AND ("ARDS" OR "acute respiratory distress syndrome" OR "acute lung injury" OR "acute respiratory failure"). We only considered English-written studies reporting pulmonary vascular resistance (PVR) or PVR index in mechanically-ventilated patients with ARDS. We excluded studies on pediatric patients only, studies on animals, reviews, case reports, studies not reporting hemodynamic measurements. When it was evident that the same patients were included in more than one study, we considered only the larger one.

The study was approved by the Ethics Committees of the Istituto Auxologico Italiano, Milan, and Ospedale Papa Giovanni XXIII, Bergamo, Italy (HEMO-COVID protocol). Informed consent for the anonymized use of clinical data for research purposes was waived because the patients were unconscious and in critical conditions, and due to the impossibility to have a physical contact with their relatives. Researchers analyzed only deidentified (anonymized) data.

Conversely, all controls signed a written informed consent for their clinical data to be used for research purposes.

Echocardiography

An experienced echocardiographer performed 2-dimensional and Doppler echocardiography studies following current recommendations [19]. Images were stored in digital format for quantitative analysis blinded to hemodynamic data. LV geometry was assessed using 2-dimensional echocardiography in parasternal long-axis view [19]. Representative echocardiographic images are reported in the online data supplement. Only the echocardiographic studies performed within 24 hours from the hemodynamic assessment were considered.

Right heart catheterization

A 7-F fluid-filled Swan-Ganz catheter was placed in the pulmonary artery through the right internal jugular vein by 2 skilled operators at each center, who then performed hemodynamic readings (LG

and FR at Ospedale Papa Giovanni XXIII, and SC and CB at Istituto Auxologico Italiano). The transducer was zeroed at the midthoracic line, halfway between the anterior sternum and the bed surface [20]. Proper pulmonary artery wedge positioning was confirmed by the appearance of a typical pulmonary artery wedge pressure (PAWP) trace and by an oxygen saturation sampled at the tip of the wedged catheter 5% than arterial oxygen saturation. Pulmonary hemodynamic measures were averaged throughout several heartbeats and respiratory cycles. The shrout-fleiss intraclass correlation (ICC) was calculated in a subsample of our dataset to assess the interrater reliability of mean PAWP.

Cardiac output was measured either by direct Fick method (controls) or by using Vigilance Monitor II, Edwards Lifescience Irvine, CA (ventilated COVID-19 patients). Two milliliters of blood were simultaneously sampled from the tip of the Swan-Ganz catheter and from the radial artery for blood gas analyses. Detailed methods on the measurements and calculation of Qs/Qt and static lung compliance are reported in the online data supplement. Complete hemodynamic measurements were taken in triplicate and then averaged.

Statistics

The data are expressed as median (interquartile range) or as absolute numbers and percentage, where appropriate. Distribution of variables in terms of proximity to the normal curve and the homogeneity of variances were detected by Shapiro-Wilk test and Bartlett test, respectively. Numerical variables were analyzed with t test or Wilcoxon rank sum, according to their distributions. Categorical variables were analyzed with Chi-squared test or Fisher exact test in case of small cell sizes. Correlation analysis was performed with the Pearson product-moment. The data of main hemodynamic characteristics found in the literature were pooled by random effect models. We then used a T-test to compared the mean of our data with pooled mean. An level of 0.05 was used for all hypothesis tests. All data analyses were performed using R Core Team (2019), Vienna, Austria.

RESULTS

Clinical characteristics and echocardiographic parameters

COVID-19 patients

Between February 25th and April 15th, 2020, 255 consecutive patients with radiologically- and laboratory-confirmed COVID-19 pneumonia were admitted to the intensive care units of the two institutions. Fifty-five (21.6%) of them underwent right heart catheterization. Out of these 55 patients, 22 (40%) had complete clinical, respiratory and hemodynamic data. After having excluded one patient with bilateral pulmonary embolism, our final cohort included 21 patients (**e-figure 1**, online data supplement). Demographics and clinical characteristics of these 21 patients are reported in **Table 1**. The mean age was 65 years, the majority of patients were men (86%), overweight, 38% were obese. Most of patients were hypertensive (62%), 43% had diabetes mellitus, and only 5% had renal dysfunction. They had no previous history of cardiac disease or heart failure.

The great majority of patients had a relevant respiratory compromise, as witnessed by a Berlin score of moderate or severe ARDS in 95% of them (moderate: 52%; severe 43%). Median APACHE IV score was 57 [47-67], with an estimated mortality rate of 40.7% [29.8-51.5].

Patients with COVID-19 spent in median 6 [5-11] days with symptoms at home before hospital admission and 4 [1-7] days in hospital before endotracheal intubation. Sixty-two percent of patients received non-invasive ventilation for 4 [1-8] days before endotracheal intubation. Right heart catheterization was performed in median 3 [2-7] days after admission to the Intensive Care Unit.

Medical treatment at the time of hemodynamic assessment included antiretroviral agents, steroids, antibiotics, hydroxychloroquine, and low-molecular weight heparin (**Table 2**). Sixty-two percent of patients were treated with intravenous furosemide (median daily dose 40 mg). Twenty-eight percent of patients were treated with vasopressors.

Blood tests at the time of the hemodynamic assessment reflected the systemic inflammatory status, with mildly elevated C-reactive protein and d-dimer values, leukocytosis and mild anemia. High-sensitivity troponin was mildly increased (**Table 2**).

Clinically-indicated angio-CT of the chest was performed in 11/21 patients, revealing pulmonary embolism in 3 of them. One patient presented with involvement of one segmental and one sub-segmental pulmonary artery at the angio-CT 6 days before the hemodynamic study. Another had involvement of segmental pulmonary arteries of only one lobe at the angio-CT performed 3 days before the hemodynamic study. The last patient showed segmental and subsegmental pulmonary embolism 13 days before the hemodynamic study, with complete resolution of the obstruction at the angio-CT two days after the hemodynamic study.

Echocardiographic data were available in 13 COVID-19 patients (**Table 3**). LV ejection fraction was > 50% in all of them. LV wall thickness was increased, mainly due to concentric remodeling, which was present in 77% of patients. Left atrial dilation was present in only one patient. The right ventricle was normally sized with normal systolic function.

Characteristics of mechanical ventilation and gas exchange data at the time of cardiac catheterization are reported in **Table 4**. Static lung compliance was low (31 [24-42] mL/cmH_2O) and inversely related (r=-0.54, p=0.012) to the duration of the disease (i.e the longer the duration of symptoms, the lower the lung compliance).

Control group, non-ventilated subjects

Out of 69 patients who underwent right heart catheterization for unexplained dyspnea, we could find 21 age-, sex- and BMI- matched controls for COVID-19 patients. Demographic and clinical characteristics of control patients are summarized in **Table 1**. Three of them had a previous hospitalization for HF, four had persistent or permanent atrial fibrillation, and eight had a history of mild chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease class 1). Median NTproBNP of the control cohort was 117 [47-408] ng/L.

Echocardiography parameters of control patients are summarized in **Table 3**. Cardiac chambers showed normal size and function. Five patients (24%) showed concentric remodeling of the LV, and 2 (10%) showed concentric LV hypertrophy, whereas 66% of controls showed normal LV geometry.

Eighty-one percent of controls had hemodynamic parameters at rest within normal limits (**Table 5**).

Comparison between COVID-19 group and control group

Patients with COVID-19 patients were more diabetic, had less atrial fibrillation and had lower levels of hemoglobin (10.3 [8.6-11.5] vs 13.5 [12.7-15.1] g/dL, p<0.001) than controls (**Table 1**). Moreover, COVID-19 patients had higher LV ejection fraction, higher incidence of concentric LV remodeling, and smaller left atrial volumes than controls (**Table 3**) despite a non-significantly higher prevalence of arterial hypertension in controls.

Complete hemodynamic data are displayed in **Table 5**. Intra-class correlation coefficient in PAWP readings was 0.98.

The Qs/Qt of COVID-19 patients was 0.35 [0.28-0.45], which was significantly higher than that of controls. Qs/Qt was inversely related to static lung compliance (r=-0.57, p=0.011, **e-Figure 2**) but not to the ratio between the arterial partial pressure and the inspired fraction of oxygen (r=0.36, p=0.120).

Pulmonary artery pressure (PAP) was higher in COVID-19 patients than in controls (Table 5), with mean PAP 25 mmHg in 76% of COVID-19 patients vs 19% of controls (p<0.001). Pulmonary vascular resistance (PVR) was similar in COVID-19 patients and in controls (p=0.343). No patients either in the COVID-19 or in the control group had PVR > 3 WU. PVR was not related to Qs/Qt (r=0.21, p=0.388).

Cardiac output and heart rate were higher and systemic vascular resistance was lower in COVID-19 patients than in controls. In COVID-19 patients, total cardiac output was directly related to Qs, i.e. the amount of shunted blood (r=0.71, p<0.001), but not to hemoglobin levels (r=0.33, p=0.141).

Pulmonary hypertension was post-capillary (PAWP 15 mmHg) in 57% of COVID-19 patients and 19% of controls (p=0.011). In COVID-19 patients, PAWP was inversely related to lung compliance (r=-0.46, p=0.038, **Figure 2**). Right atrial pressure (RAP) and the ratio between RAP and PAWP were higher in COVID-19 patients than in controls (**Table 5**). Results did not change when we excluded the three COVID-19 patients with documented segmental or subsegmental pulmonary embolism (**e-tables 1-5, online data supplement**).

Control group, pooled-analysis of hemodynamics in ARDS patients from literature

Out of 1759 literature results, 58 studies reporting either PVR or PVRI were considered in this analysis (**e-Table 6**; complete article list of this systematic review is available in the online data supplement). They included 1937 patients with ARDS, whose mean age was 48.3 years (based on data available from 52 studies on 1578 patients). Sixty-three percent patients were males (based on data available from 36 studies on 1292 patients). ARDS etiology was infectious (bacterial, viral or fungal) pneumonia in 31.5% of cases (based on data available from 51 studies on 1441 patients). In all studies but one patients received standard intensive care unit treatment for ARDS according to clinical needs, including vasoactive and cardioactive drugs, fluids, sedatives. Only 10 patients out of 1937 were not mechanically-ventilated, while only 15 patients were assessed during extracorporeal membrane oxygenation. The pooled mean for relevant ventilatory and hemodynamic variables is reported in **Table 6**.

Comparison between COVID-19 group and pooled data of ARDS patients from literature

As compared with pooled data from literature, our COVID-19 patients had a similar ARDS severity as reflected by non-different positive end-expiratory pressure support (p=0.330), lung compliance (p=0.691), as well as the ratio between arterial oxygen partial pressure and inspired oxygen fraction (p=0.560). In spite of this, PVR and PVR index were lower (p<0.001 and p=0.002, respectively) while PAWP was higher (p=0.024) in our COVID-19 patients than in pooled ARDS patients from literature. Cardiac output and systemic vascular resistance were not different between the two groups (p=0.411 and p=0.182, respectively), while cardiac index and systemic vascular resistance index were higher in COVID-19 patients (p=0.024 and p=0.013, respectively).

Survivors vs non-survivors

Eleven COVID-19 patients (52%) died in the ICU and ten survived. The patients who died, as compared to survivors, had similar age (p=0.223), sex distribution (p=0.476) and BMI (p=0.672). As shown in **e-Table 7, online data supplement**, they were ventilated with higher inspired oxygen fraction (0.80 [0.75-0.88] vs 0.68 [0.46-0.70], p=0.025) and higher plateau pressure (28 [27-30] vs 23 [21-25] cmH_2O, p=0.005), whereas lung compliance was similar (28 [21-39] vs 34 [27-43] mL/cmH_2O, p=0.387). COVID-19 patients who died had a trend towards higher Qs/Qt (0.43 [0.34-0.49] vs 0.30 [0.28-0.35], p=0.079), had higher Qs (3.5 [2.6-4.0] vs 1.9 [1.6-2.3] L/min, p=0.016) and cardiac output (4.1 [3.4-4.6] vs 2.7 [2.4-3.7] $L/min/m^2$, p=0.051), as shown in **e-Table 8, online data supplement**. Consequently, mean PAP was higher in non-survivors as compared with survivors (31 [27-37] vs 25 [18-27] mmHg, p=0.032) despite non-significantly higher PAWP (16 [13-18] vs 13 [11-20] mmHg, p=0.397) and PVR (2.1 [1.3-2.6] vs 1.4 [0.8-2.2] WU, p=0.387).

DISCUSSION

To the best of our knowledge, our study is the first to report invasive hemodynamic characteristics of mechanically-ventilated COVID-19 patients with ARDS. In particular, our COVID-19 patients seemed to present peculiar hemodynamic features, as outlined by *i.* only mild increase of PAP with surprisingly low PVR despite respiratory failure; and *ii*. high prevalence of increased LV filling pressures. Both these elements, either due to coronavirus itself or to the characteristics of infected patients (elderly subjects with cardiovascular comorbidities), in the context of an inflammation-driven hyperdynamic circulation, might contribute to clinical manifestations, promoting

a vicious circle between the heart and the lungs (**central figure**). In particular, in this specific context, low PVR might facilitate both the development of high LV pressure as well as lung congestion and stiffening, since LV preload is not impeded and the capillary membrane is not protected by a pre-capillary resistor.

Respiratory characteristics of our COVID-19 patients would suggest, at a first glance, a “typical” form of ARDS, the so-called “type H” COVID-19 pneumonia [21]. Static lung compliance was roughly one third of normal values, which is coherent with previous data on ARDS in non-COVID-19 patients, reflecting extensive parenchymal disruption, changes in surfactant due to virus infection, as well as the severity of the respiratory failure [22].

Indeed, ARDS is generally believed to be characterized by high PVR due to hypoxic pulmonary vasoconstriction in pulmonary units with low alveolar oxygen pressure [5]. This reflex vascular modulation can reduce blood flow to atelectatic regions by 50%, with a significant improvement of ventilation/perfusion ratio [23] and may limit the intrapulmonary shunt, whereby increasing right ventricular afterload. Conversely, PVR was “atypically” low in our COVID-19 patients with ARDS, and not significantly different from measurements obtained in control patients without ARDS. In this perspective, our data seem to confirm the hypothesis that COVID-19 might be associated with a blunted hypoxic pulmonary vasoconstriction [7-9], even when pulmonary compliance is low and lung damage is relevant. This may occur through several purely speculative virus-induced mechanisms, including: up- or down-regulation of mitochondrial proteins involved in aerobic metabolism [24], with a consequent interference with O_2 sensing [8]; COVID-19 related pulmonary neoangiogenesis [25]; dysregulated ACE2 metabolism [26] and/or inflammatory stimuli with a potential imbalance between vasodilatory and vasoconstrictor substances/substrates leading to a net effect of low PVR.

Clinical characteristics of coronavirus-infected patients, including age and cardiovascular comorbidities, might also contribute to this “atypical” presentation, characterized by more marked pulmonary than systemic vasoplegia and high LV filling pressure, as compared with “typical” ARDS. Indeed, in elderly subjects, high cardiac output can be easily associated with high LV filling pressure [27], especially if low pulmonary vascular tone does not impede LV preload. Obviously, not only local pulmonary but also systemic factors, such as cytokine storm, anemia and hypercapnia, might contribute to this high-output state, as it is generally the case in the context of

ARDS. Additionally, the peculiar neurotropism of coronavirus might also play a role, accounting for alterations of normal cardiovascular reflexes [28].

Coherently with low PVR, also mean PAP was only mildly elevated in COVID-19 patients, and such increase was totally explained by high cardiac output and high PAWP [29]. Interestingly, pulmonary hypertension was present in more than half of patients and was always post-capillary [30], and occurred in spite of a large use of intravenous diuretics at high dose. The non pre-conditioned right ventricle of COVID-19 patients behaved as expected, with a still preserved contractility without overt dilation to face an acutely increased afterload (homeometric adaptation) [31]. However, it has been repeatedly demonstrated that a higher than normal PAWP can increase the pulsatile afterload of the RV in spite of normal PVR [32]. Thus, despite a still preserved RV morphology and function, which is at variance from previous reports including patients with acute pulmonary embolism during COVID-19 [13], RAP was already increased in our patients, with a high ratio between RAP and PAWP, portending right heart failure, which is coherent with the evidence of liver congestion, associated with lung congestion, in a number of COVID-19 patients who underwent autopsy at Papa Giovanni XXIII Hospital (unpublished data). However, we cannot exclude technical limitations in measuring the RV in mechanically-ventilated patients, due to exquisite sensitivity of right ventricular size with angular change [19]. Alternatively, we might hypothesize that the mild RAP increase we found in COVID-19, associated with high RAP/PAWP ratio, could reflect enhanced ventricular interdependence in mechanically-ventilated patients, as a result of reduced lung compliance and high PEEP [33]. Indeed, also enhanced ventricular interdependence can be associated with high filling pressures and mildly elevated PAP, further exacerbated by increased metabolic demands [34].

The finding of mildly elevated PAWP in our population of COVID-19 patients deserves particular attention. Firstly, pathological specimens from patients with ARDS frequently reveal diffuse alveolar damage, with both alveolar epithelial and lung endothelial injury, resulting in accumulation of protein-rich inflammatory edematous fluid in the alveolar space [5]. In this specific setting, a higher than normal PAWP may further promote interstitial and alveolar edema [35]. This might help explaining the association between PAWP and lung compliance, suggesting that high PAWP may further contribute to worsen lung stiffness. Secondly, high PAWP is a hallmark of heart failure. All of our COVID-19 patients, albeit burdened with a number of cardiovascular risk factors, did not have a previous history of heart failure. However, a number of otherwise healthy elderly people might present with “pathologically” high PAWP during high-output states [27], basically unmasking

age-related LV stiffening, but potentially exposing the pulmonary capillary membrane to damage and interstitial edema [35]. This behavior might be further exacerbated by the presence of risk factors associated with cardiovascular ageing, even in the absence of LV hypertrophy or other overt cardiac abnormalities [36]. Indeed, our COVID-19 patients were quite systematically found to present with LV concentric remodeling. We may hypothesize that this finding could simply reflect the limits of fine echocardiographic measurements in challenging conditions such as that encountered in mechanically-ventilated patients with a hyperdynamic circulation. Additionally, LV concentric remodeling is not a necessary condition to develop high filling pressure during increased metabolic demands [34,35]. Moreover, arterial hypertension, which is a common comorbidity in COVID-19 patients and could have been underdiagnosed, might have played a pre-existing role on LV geometry changes. Finally, we cannot exclude that coronavirus-2 might have contributed to LV remodeling: COVID-19 has been associated with decreased expression of ACE2 receptor in the heart [10,37], that might accelerate LV remodeling [26], especially on the background of a hyperdynamic state. According with an acute process affecting the LV, the left atrium, which generally acts as a pressure buffer and dilates over time when LV end-diastolic pressure increases [36], was within normal limits, and even smaller than our control group. On the other hand, a direct myocardial injury by coronavirus-2 [11], with consequent myocardial edematous changes [38], seems unlikely in our cohort, based on only mildly elevated troponin and supernormal LV systolic function, which is at variance from previous reports occasionally indicating various degree of LV involvement during COVID-19 [12,13].

Study limitations

We enrolled a limited, but well phenotyped, cohort of COVID-19 patients that, in the frame of the peculiar allocation of resources during the outbreak of COVID-19 pandemic [2], underwent invasive hemodynamic assessment in randomly assigned, dedicated beds of the cardiac surgery Intensive Care Unit. Moreover, severe respiratory or cardiovascular comorbidities were not represented in our population. Thus, we cannot exclude a potential selection bias, even if the burden of mild comorbidities was quite consistent with recently published data [4]. Furthermore, our small sample size might have prevented us from detecting other significant differences in subgroup analyses (e.g. survivors vs non-survivors).

Since pulmonary vessels and the heart are intrathoracic, mechanical ventilation can affect hemodynamic measurements. However, lung compliance in our cohort was markedly reduced,

suggesting a negligible transmission of positive end-expiratory pressure to intravascular and intracardiac compartments.

An ideal control group for our COVID-19 patients would have been composed by non-COVID-19 ARDS. However, right heart catheterization is nowadays rarely performed during ARDS. We tried to overcome this limit performing a systematic review and pooled analysis of published data. These results from 1937 ARDS from literature could corroborate and complement those obtained in the comparison of COVID-19 with matched subjects without relevant comorbidities and without obvious causes for dyspnea from our cardiac catheterization laboratory database. As such, these two groups represent the best control groups we could use: the former highly representative of the characteristics of mechanically-ventilated but younger ARDS patients, and the latter characterized by hemodynamics closer to that of elderly, otherwise healthy subjects. Accordingly, the hemodynamic profile of the control group was roughly compatible with that of an aged, overweight and hypertensive population.

CONCLUSIONS

In our small but well phenotyped cohort of mechanically-ventilated COVID-19 patients, we found some “atypical” ARDS features, either related to coronavirus itself or to the general characteristics of affected individuals (elderly patients with cardiovascular comorbidities), including a blunted hypoxic pulmonary vasoconstriction with high cardiac output and “unimpeded” high LV filling pressure. These alterations may promote a vicious circle where the increase of PAWP might contribute to lung stiffening and to the severity of the respiratory insufficiency.

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Disclosures

The authors have no conflict of interest to disclose.

REFERENCES

1. Senni M. COVID-19 experience in Bergamo, Italy. Eur Heart J. 2020 Apr 7. pii: ehaa279. doi: 10.1093/eurheartj/ehaa279. [Epub ahead of print]

2. Fagiuoli S, Lorini FL, Remuzzi G; Covid-19 Bergamo Hospital Crisis Unit. Adaptations and Lessons in the Province of Bergamo. N Engl J Med. 2020 May 21;382(21):e71. doi: 10.1056/NEJMc2011599. Epub 2020 May 5. PMID: 32369276; PMCID: PMC7219535

3. Sanfilippo F, Bignami E, Lorini FL, Astuto M. The importance of a "socially responsible" approach during COVID-19: the invisible heroes of science in Italy. Crit Care. 2020 May 26;24(1):261. doi: 10.1186/s13054-020-02998-0. PMID: 32456692; PMCID: PMC7250282..

4. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020 Apr 6. doi: 10.1001/jama.2020.5394. [Epub ahead of print]

5. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. N Engl J Med. 2017 Aug 10;377(6):562-572. doi: 10.1056/NEJMra1608077.

6. Ryan D, Frohlich S, McLoughlin P. Pulmonary vascular dysfunction in ARDS. Ann Intensive Care. 2014 Aug 22;4:28. doi: 10.1186/s13613-014-0028-6

7. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020 Mar 30. doi: 10.1164/rccm.202003-0817LE

8. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, Li MD, Witkin A, Rodriguez-Lopez JM, Shepard JAO, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis 2020 [Epub ahead of print]

9. Archer SL, Sharp WW, Kenneth Weir E. Differentiating COVID-19 Pneumonia from Acute Respiratory Distress Syndrome (ARDS) and High Altitude Pulmonary Edema (HAPE): Therapeutic Implications.

10. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani L, et al. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease. Circulation. 2020 Mar 21. doi: 10.1161/CIRCULATIONAHA.120.046941

11. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. JAMA Cardiol. 2020 Mar 27. doi: 10.1001/jamacardio.2020.1105. [Epub ahead of print]

12. Fried JA, Ramasubbu K, Bhatt R, et al. The Variety of Cardiovascular Presentations of COVID-19. Circulation. 2020;141(23):1930-1936. doi:10.1161/CIRCULATIONAHA.120.047164

13. Szekely Y, Lichter Y, Taieb P, et al. The Spectrum of Cardiac Manifestations in Coronavirus Disease 2019 (COVID-19) - a Systematic Echocardiographic Study [published online ahead of print, 2020 May 29]. Circulation. 2020;10.1161/CIRCULATIONAHA.120.047971. doi:10.1161/CIRCULATIONAHA.120.047971

14. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. N Engl J Med. 1977 Mar 3;296(9):476-80. doi: 10.1056/NEJM197703032960903. PMID: 834225.

15. Zimmerman GA, Morris AH, Cengiz M. Cardiovascular alterations in the adult respiratory distress syndrome. Am J Med. 1982 Jul;73(1):25-34. doi: 10.1016/0002-9343(82)90920-2. PMID: 7091171.

16. Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S; Lille ICU Haemostasis COVID-19 group. Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence. Circulation. 2020 Apr 24. doi: 10.1161/CIRCULATIONAHA.120.047430. [Epub ahead of print]

17. Azarian R, Wartski M, Collignon MA, Parent F, Hervé P, Sors H, Simonneau G. Lung perfusion scans and hemodynamics in acute and chronic pulmonary embolism. J Nucl Med. 1997 Jun;38(6):980-3. PMID: 9189155.

18. Vesconi S, Rossi GP, Pesenti A, Fumagalli R, Gattinoni L. Pulmonary microthrombosis in severe adult respiratory distress syndrome. Crit Care Med. 1988 Feb;16(2):111-3. doi: 10.1097/00003246-198802000-00002. PMID: 3342622.

19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015 Mar;16(3):233-70. doi: 10.1093/ehjci/jev014

20. Caravita S, Faini A, Carolino D'Araujo S, Dewachter C, Chomette L, Bondue A, Naeije R, Parati G, Vachiéry JL. Clinical phenotypes and outcomes of pulmonary hypertension due to left heart disease: Role of the pre-capillary component. PLoS One. 2018 Jun 19;13(6):e0199164. doi: 10.1371/journal.pone.0199164

21. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes?. Intensive Care Med. 2020;46(6):1099-1102. doi:10.1007/s00134-020-06033-2

22. Henderson WR, Chen L, Amato MBP, Brochard LJ. Fifty Years of Research in ARDS. Respiratory Mechanics in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2017 Oct 1;196(7):822-833. doi: 10.1164/rccm.201612-2495CI.

23. Morrell NW, Nijran KS, Biggs T, Seed WA. Magnitude and time course of acute hypoxic pulmonary vasoconstriction in man. Respir Physiol 1995; 100: 271–281

24. Lai CC, Jou MJ, Huang SY, Li SW, Wan L, Tsai FJ, Lin CW. Proteomic analysis of up-regulated proteins in human promonocyte cells expressing severe acute respiratory syndrome coronavirus 3C-like protease. Proteomics. 2007;7:1446-1460.

25. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19 [published online ahead of print, 2020 May 21]. N Engl J Med. 2020;10.1056/NEJMoa2015432. doi:10.1056/NEJMoa2015432

26. Guo J, Huang Z, Lin L, Lv J. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. J Am Heart Assoc. 2020 Apr 7;9(7):e016219. doi: 10.1161/JAHA.120.016219. Epub 2020 Apr 1.

27. Wolsk E, Bakkestrøm R, Thomsen JH, Balling L, Andersen MJ, Dahl JS, Hassager C, Møller JE, Gustafsson F. The Influence of Age on Hemodynamic Parameters During Rest and Exercise in Healthy Individuals. JACC Heart Fail. 2017 May;5(5):337-346. doi: 10.1016/j.jchf.2016.10.012. Epub 2016 Dec 21. PMID: 28017352.

28. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. Lancet Neurol. 2020 Sep;19(9):767-

783. doi: 10.1016/S1474-4422(20)30221-0. Epub 2020 Jul 2. PMID: 32622375; PMCID: PMC7332267.

29. Reddy YNV, Melenovsky V, Redfield MM, Nishimura RA, Borlaug BA. High-Output Heart Failure: A 15-Year Experience. J Am Coll Cardiol. 2016 Aug 2;68(5):473-482. doi: 10.1016/j.jacc.2016.05.043.

30. Vachiéry JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, Coghlan G, Chazova I, De Marco T. Pulmonary hypertension due to left heart disease. Eur Respir J. 2019 Jan 24;53(1). pii: 1801897. doi: 10.1183/13993003.01897-2018

31. Vonk Noordegraaf A, Chin KM, Haddad F, Hassoun PM, Hemnes AR, Hopkins SR, Kawut SM, Langleben D, Lumens J, Naeije R. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J. 2019 Jan 24;53(1). pii: 1801900. doi: 10.1183/13993003.01900-2018

32. Tedford RJ, Hassoun PM, Mathai SC, Girgis RE, Russell SD, Thiemann DR, Cingolani OH, Mudd JO, Borlaug BA, Redfield MM, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. Circulation. 2012 Jan 17;125(2):289-97

33. Verhoeff K, Mitchell JR. Cardiopulmonary physiology: why the heart and lungs are inextricably linked. Adv Physiol Educ. 2017 Sep 1;41(3):348-353. doi: 10.1152/advan.00190.2016.

34. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation. 2017 Jul 4;136(1):6-19. doi: 10.1161/CIRCULATIONAHA.116.026807. Epub 2017 Apr 5. PMID: 28381470; PMCID: PMC5501170.

35. Reddy YNV, Obokata M, Wiley B, Koepp KE, Jorgenson CC, Egbe A, Melenovsky V, Carter RE, Borlaug BA. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. Eur Heart J. 2019 Dec 1;40(45):3721-3730. doi: 10.1093/eurheartj/ehz713.

36. Senni M, Caravita S, Paulus WJ. Do Existing Definitions Identify Subgroup Phenotypes or Reflect the Natural History of Heart Failure With Preserved Ejection Fraction? Circulation. 2019 Jul 30;140(5):366-369. doi: 10.1161/CIRCULATIONAHA.119.041657. Epub 2019 Jul 29.

37. Oudit GY, Pfeffer MA. Plasma angiotensin-converting enzyme 2: novel biomarker in heart failure with implications for COVID-19. Eur Heart J 2020, ehaa414, https://doi.org/10.1093/eurheartj/ehaa414

38. Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac involvement in recovered COVID-19 patients identified by magnetic resonance imaging. J Am Coll Cardiol Img. 2020 May 11. Epublished DOI:10.1016/j.jcmg.2020.05.004

Table 1. Demographics, anthropometrics and clinical characteristics of COVID-19 patients with acute respiratory distress syndrome requiring mechanical ventilation, and controls

	COVID-19 (n= 21)	Controls (n= 21)	p-value
Demographics and anthropometrics			
Age, years	67 [60-70]	71 [66-75]	0.144
Male sex, n (%)	18 (86)	18 (86)	1.00
BMI, Kg/m^2	29 [25-31]	27 [26-33]	0.783
BMI 25-30 Kg/m^2 n (%)	9 (43)	10 (48)	0.757
BMI 30 Kg/m^2 n (%)	8 (38)	8 (38)	1.000
Previous medical history			
Arterial hypertension, n (%)	13 (62)	17 (81)	0.171
Diabetes mellitus, n (%)	9 (43)	2 (10)	0.014
Dyslipidemia, n (%)	3 (14)	9 (43)	0.040
Chronic kidney disease, n (%)	1 (5)	0	0.312
COPD, n (%)	1 (5)	8 (38)	0.008
Cerebrovascular disease, n (%)	1 (5)	2 (10)	0.549
Coronary artery disease, n (%)	3 (14)	6 (29)	0.259
Heart failure, n (%)	0	2 (10)	0.147
Atrial fibrillation, n (%)	0	4 (19)	0.036
Immunological disorder, n (%)	1 (5)	0	0.312
Smoking habitus, n (%)	1 (5)	1 (5)	1.000

Continuous variables are shown as medians [Interquartile range]

Abbreviations: BMI=body mass index; COVID-19=2019 novel coronavirus disease; COPD=chronic obstructive pulmonary disease

Table 2. Pharmacological treatment and blood tests at the time of the right heart catheterization.

	COVID-19 (n= 21)
Medical treatment in the Intensive Care Unit	
Antiretroviral agents, n (%)	6 (29)
Steroids, n (%)	15 (71)
Antibiotics, n (%)	15 (71)
Hydroxicloroquine, n (%)	6 (29)
Low molecular weight heparin	
Parenteral anticoagulation, n (%)	14 (67)
Thromboembolic prophylaxis, n (%)	7 (34)
Adrenergic agents	
Norepinephrine alone, n (%)	3 (14)
Norepinephrine + adrenaline, n (%)	3 (14)
Norepinephrine dose (mcg/kg/min)	0.07 [0.04-0.1]
Furosemide	
n (%)	13 (62)
Dose, mg	40 [30-120]
Blood tests	
High-sensitivity troponin, ng/mL	23 [6-94]
Hemoglobin, g/dL	10.3 [8.6-11.5]
Creatinine, mg/dL	0.8 [0.6-1.1]
Azotemia, mg/dL	56 [39-82]
White blood cells, 10^3/mcL	10.3 [7.0-15.4]
C-reactive protein, mg/dL	12.7 [2.7-19.0]
Procalcitonin, mg/mL	0.6 [0.2-1.8]
D-dimer, ng/mL	1470 [1057-2384]
Fibrinogen, mg/dL	564 [372-681]

Table 3. Echocardiographic data.

	COVID-19 (n= 13)	**Controls (n= 21)**	**p-value**
LV EDV, mL	109 [95-119]	101 [89-110]	0.395
LV EF, %	67 [61-72]	64 [60-65]	<0.001
IVS thickness, mm	12 [11-13]	11 [10-12]	0.024
PW thickness, mm	11 [10-11]	10 [9-11]	0.045
LV mass, g/m^2	88 [75-108]	89 [80-102]	0.915
LV RWT, cm	0.46 [0.43-0.54]	0.40 [0.38-0.44]	0.008
LV geometry			<0.001
Normal geometry, n (%)	0 (0)	14 (66)	
Concentric remodeling, n (%)	10 (77)	5 (24)	
Concentric hypertrophy, n (%)	1 (8)	2 (10)	
Eccentric hypertrophy, n (%)	2 (15)	0 (0)	
LAVI, mL/m^2	24 [22-28]	30 [27-46]	0.007
RV basal diameter, mm	36 [32-38]	40 [36-43]	0.151
RV/LV ratio	0.8 [0.7-0.9]	0.8 [0.7-1.0]	0.567
RV EDA, cm^2	21 [19-23]	18 [16-22]	0.249
RV FAC, %	42 [40-56]	47 [43-49]	0.669
TAPSE, mm	22 [17-26]	25 [21-27]	0.463
S' RV wave, cm/sec	14 [13-16]	15 [13-15]	0.481
RAVI, mL/m^2	21 [15-29]	32 [18-38]	0.220

Abbreviations: EDV=end-diastolic volume; EF=ejection fraction; EDA= end-diastolic area; FAC=fractional area change; IVS=interventricular septum; LAVI=left atrial volume index; LV=left ventricle; PW=posterior wall; RWT=relative wall thickness; RV=right ventricle; RAVI=right atrial volume index TAPSE=tricuspid annular plane systolic excursion. Other abbreviations as in Table 1.

TABLE 4. Mechanical ventilation characteristics and gas-exchange data

	COVID-19 patients	Control group	p-value
Mechanical ventilation			
FiO_2, %	70 [60-80]	-	-
PEEP, cmH_2O	11 [8-14]	-	-
Peak inspiratory pressure, cmH_2O	28 [25-32]	-	-
Plateau pressure, cmH_2O	27 [23-29]	-	-
Tidal volume, mL	470 [360-520]	-	-
Respiratory rate, /min	24 [20-28]	-	-
Static lung compliance, mL/cmH_2O	31 [24-42]	-	-
Gas exchange			
Arterial pH	7.40 [7.33-7.44]	-	-
$PaCO_2$, mmHg	57 [43-66]	39 [36-43]	<0.001
PaO_2, mmHg	74 [69-93]	89 [76-95]	0.106
SaO_2, %	95 [93-96]	96 [94-97]	0.174
Lactate, mmoL/L	1.1 [1.0-1.6]	0.7 [0.6-0.8]	<0.001
PvO_2, mmHg	43 [39-48]	38 [37-40]	0.091
SvO_2, %	73 [68-77]	71 [67-73]	0.371
PaO_2/FiO_2, mmHg	103 [83-153]	424 [361-451]	<0.001
CaO_2, mL/dL	14.4 [12.8-16.7]	18.4 [17.4-19.9]	<0.001
CvO_2, mL/dL	11.2 [10.0-12.3]	13.7 [12.3-14.8]	<0.001
$C(a\text{-}v)O_2$, mL/dL	3.3 [2.9-3.9]	4.8 [4.5-5.3]	<0.001

Abbreviations: CaO_2=arterial oxygen content; $C(a\text{-}v)O_2$=artero-venous oxygen difference; CvO_2=venous oxygen content; FiO_2=inspired oxygen fraction; $PaCO_2$=arterial partial pressure for carbon dioxide; PaO_2=arterial partial pressure for oxygen; PEEP=positive end-expiratory pressure; PvO_2=venous partial pressure for oxygen; SaO_2=arterial oxygen saturation. Other abbreviations as in Table 1.

TABLE 5. Invasive hemodynamic data.

	COVID-19 patients	Control group	p-value
Cardiac output and shunt fraction			
Heart rate, bpm	89 [72-94]	65 [58-78]	<0.001
Cardiac output, L/min	7.3 [5.3-8.8]	4.5 [3.9-5.5]	<0.001
Stroke volume, mL	83 [68-105]	69 [59-90]	0.088
Cardiac index, L/min/m^2	3.8 [2.7-4.5]	2.4 [2.1-2.8]	<0.001
Qs/Qt	0.35 [0.28-0.45]	0.13 [0.06-0.17]	<0.001
Systemic hemodynamics			
Systolic BP, mmHg	124 [110-143]	140 [134-148]	0.208
Diastolic BP, mmHg	62 [48-71]	78 [66-80]	0.007
Mean BP, mmHg	82 [70-100]	101 [90-103]	0.017
Systemic Vascular Resistance, WU	9.5 [8.1-13.0]	18.4 [14.1-23.2]	0.014
Pulmonary and right heart hemodynamics			
Systolic PAP, mmHg	41 [34-48]	25 [22-34]	<0.001
Diastolic PAP, mmHg	20 [15-26]	14 [10-16]	<0.001
Mean PAP, mmHg	27 [25-33]	17 [14-21]	<0.001
PAWP, mmHg	15 [11-18]	9 [8-13]	0.012
RAP, mmHg	11 [9-15]	5 [4-7]	<0.001
RAP/PAWP	0.8 [0.7-0.9]	0.5 [0.4-0.7]	0.004
PAWP – RAP, mmHg	3 [2-6]	4 [3-7]	0.370
Pulmonary Vascular Resistance, WU	1.6 [1.1-2.5]	1.6 [0.9-2.0]	0.343
Total Pulmonary Resistance, WU	4.0 [3.1-4.7]	3.9 [2.5-5.3]	0.537
Diastolic pressure gradient, mmHg	5 [0-8]	2 [1-3]	0.047
Transpulmonary pressure gradient, mmHg	13 [8-14]	6 [5-8]	0.002
Mean PAP 25 mmHg, n (%)	16 (76)	4 (19)	<0.001
PVR > 3 WU	0	0	1.000
Post-capillary PH, n (%)	12 (57)	4 (19)	0.011
Isolated post-capillary PH, n (%)	12	4	
Combined post- and pre-capillary PH, n (%)	0	0	

Abbreviations: BP=blood pressure; PAP=pulmonary artery pressure; PAWP=pulmonary artery wedge pressure; PH=pulmonary hypertension; PVR=pulmonary vascular resistance; Qs/Qt=intrapulmonary shunt; RAP=right atrial pressure. Other abbreviations as in Table 1.

Table 6. Cardiorespiratory profile of ARDS patients from literature

	Studies, n	Subjects, n	Pooled mean	Confidence interval
PaO2/FiO2, mmHg	43	1568	127	117-138
Qs/Qt	35	1147	0.36	0.33-0.39
Static lung compliance, mL/cmH2O	21	528	34	31-37
PEEP, cmH2O	33	1389	10.2	9.3-11.2
Mean PAP, mmHg	66	1832	31	30-32
PAWP, mmHg	46	1580	13	12-13
CO, L/min)	16	261	6.9	6.3-7.5
CI, L/min/m2)	43	1362	4.3	4.1-4.4
PVR, WU	38	586	2.9	2.6-3.2
PVRI, mmHg/L/min/m2	34	1351	4.6	4.1-5.0
SVR, WU	18	231	9.9	8.8-11.0
SVRI, mmHg/L/min/m2	17	1043	17.1	15.6-18.6

Abbreviations: CI=cardiac index; CO=cardiac output; FiO2=inspired oxygen fraction; PaO2=arterial partial pressure for oxygen; PEEP=positive end-expiratory pressure; PAP=pulmonary artery pressure; PAWP=pulmonary artery wedge pressure; PVR=pulmonary vascular resistance; PVRI=pulmonary vascular resistance index; Qs/Qt=intrapulmonary shunt; SVR=systemic vascular resistance; SVRI=systemic vascular resistance index.

FIGURES LEGEND

Figure 1. Inverse relationship between lung compliance and pulmonary artery wedge pressure. PAWP=pulmonary artery wedge pressure.

Central Figure. Vicious circle between the lung and the heart in COVID-19. Coronavirus-2 causes an interstitial pneumonia characterized by low lung compliance. The ventilation perfusion-mismatch of non-ventilated but perfused lung zones is enhanced by specific virus-related mechanisms, with blunted hypoxic pulmonary vasoconstriction and normal pulmonary vascular resistance, further promoting the intrapulmonary shunt. High cardiac output due to acute inflammation and hypoxemia, with low PVR and unimpeded left ventricular preload, predisposes to high filling pressure, which might be favored by patients' characteristics (elderly with cardiovascular comorbidities) and further exacerbated by virus-related cardiac remodeling. High left ventricular filling pressure promotes lung congestion with further reduction of lung compliance. ACE=angiotensin-converting enzyme; C_{STAT}=static lung compliance; LV=left ventricle; PAWP=pulmonary artery wedge pressure; PVR=pulmonary vascular resistance; Qs/Qt=intrapulmonary shunt; SIRS=systemic inflammatory response syndrome.