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Original Article

Cardiac involvement in critically ill and mechanically ventilated patients with COVID-19 - a prospective, observational echocardiographic study

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Abstract: Introduction: In this prospective, observational study, we have evaluated right (RV) and left (LV) ventricular function with echocardiography and correlated it to the levels of biomarkers, hs-TNT, NT-pro-BNP, D-dimer and fibrinogen. In a subgroup, we have evaluated the effect of inhaled milrinone on RV afterload and function. Methods: Thirty-one ICU patients with COVID-19 in need of mechanical ventilation and norepinephrine infusion were prospectively included. Hemodynamic and respiratory variables were measured at the time of the echocardiographic examination and biomarkers were obtained on arrival at the ICU and then followed up routinely. Eight patients received inhaled aerosolized milrinone at a dose of 2.5 mg/hour. Results: The most common echocardiographic pattern was RV dilation with or without systolic dysfunction, which was found in 62% of patients. Pulmonary acceleration time was abnormal in 55% and indices of RV systolic function, such as fractional area of change, RV strain, were abnormal in 30% and 31% of patients respectively. A cardiac index of < 2.5 l/minxm^2 was seen in 58% of the patients. Left ventricular ejection fraction and global left ventricular strain were impaired in 10% and 16% respectively. The correlation between echocardiographic variables and cardiac biomarkers was poor. RV afterload correlated well to the levels of D-dimer. Milrinone inhalation did not improve RV function or afterload. Conclusion: RV dysfunction was the most common finding. The poor correlation to cardiac biomarkers argues against extensive myocardial involvement. The lack of improvement in RV function after milrinone inhalation suggests that the most likely cause of RV dysfunction is increased RV afterload caused by pulmonary thrombosis/embolism.

Keywords: COVID-19, intensive care unit, right ventricular failure, inhalation of milrinone, D-dimer

Introduction

Coronavirus infection disease has caused considerable mortality and morbidity worldwide. Cardiac involvement is often registered in hospitalized patients with a reported incidence ranging between 14-40% [1, 2]. Currently published data suggest that cardiovascular manifestations of COVID-19 can involve high blood pressure, arrhythmias, biomarker elevation, LV and RV dysfunction, or even cardiogenic shock [3-5]. Cardiac complications of COVID-19 are associated with a poorer prognosis, including increased ICU admission and mortality [6]. Data from a recent study indicated that patients with cardiac injury had higher mortality than those without cardiac injury (51.2% vs 4.5% respectively) [7]. Whether heart failure in COVID-19 patients is primarily a result of the exacerbation of underlying undiagnosed cardiomyopathy, myocarditis, or a new cardiomyopathy secondary to a robust proinflammatory cytokine storm remains an area of active research.

Acute RV failure in the ICU is a condition associated with substantial morbidity and mortality [8, 9]. High-risk patients include those with sepsis, acute respiratory distress syndrome (ARDS) or after cardiac surgery [10, 11]. The

syndrome can often be confirmed with echocardiography. In ICU patients with RV dysfunction with hemodynamic instability, treatment with vasopressors, inotropes, the inhalation of nitric oxide or inodilators, such as prostacyclin analogs or milrinone, may be indicated. Recently, studies of patients hospitalized due to COVID-19 infection have demonstrated prevalent RV dilation [12-15]. One study showed that the impairment of RV systolic function and LV diastolic dysfunction correlated strongly with both elevated troponin and a poorer clinical outcome after hospitalization [16]. However, most of these studies that base their results on echocardiographic data do not distinguish between patients who are intubated and mechanically ventilated and those who are not and this makes the results difficult to interpret.

As a result, the aim of the present study was to evaluate RV and LV function in intubated ICU patients with COVID-19. We also aimed to investigate the association between echocardiographic parameters and the biomarkers of D-dimer, fibrinogen and hsTNT in this group of patients. Finally, in a subgroup of patients with pulmonary hypertension and RV dysfunction, the effects of inhaled milrinone on RV systolic function was evaluated.

Methods

Study population

This study was approved by the Swedish Ethical Review Authority (approval number 2020-02756) which waived the need for informed consent due to the patients' severe health condition. All the patients were intubated when admitted to our ICU.

We prospectively included 31 patients admitted to the ICU at Sahlgrenska University Hospital/Mölndal, between 02/04/2020 and 22/05//2020. The inclusion criteria were: 1) age ≥ 18 years old 2) they had a verified COVID-19 infection and the diagnosis was confirmed by a positive reverse-transcriptase-polymerase chain reaction assay for SARS-CoV-2 from a respiratory tract sample 3) all patients were intubated and in need of mechanical ventilation. The exclusion criteria were: a) ongoing atrial fibrillation or flutter b) patients with a pacemaker and c) patients previously diagnosed with hypertrophic, dilative or ischemic cardiomyopathy.

In each patient, hemodynamic and respiratory variables were recorded at the time of the echocardiographic examination. The following respiratory parameters were recorded: fractional inspired oxygen (FiO_2), positive end-expiratory pressure (PEEP), oxyhemoglobin saturation (SaO_2), tidal volume and respiratory rate. Further, systolic and mean arterial (MAP) pressures were measured invasively from a radial artery catheter and, finally, the simplified acute physiology score (SAPS) was recorded in all patients on ICU arrival.

A subgroup of eight patients received a milrinone inhalation due to respiratory derangement. The indication to initiate inhalations of milrinone was supported by the need for a high FiO_2 of > 60% combined with right ventricular overload. None of these patients was exposed to a milrinone inhalation before the first echocardiographic examination and the decision to start the treatment was taken by the physician in charge. Inhaled milrinone was administered continuously at a dose of 2.5 mg/hour and its effect on RV function and hemodynamics was monitored by repeated echocardiographic examinations.

Biomarkers

Blood samples for the cardiac biomarkers of high-sensitive troponin-T (hsTnT), N-terminal pro B-type natriuretic peptide (NT-proBNP) and the thromboembolic biomarkers fibrinogen and D-dimer were collected upon arrival at the ICU and followed up regularly.

Echocardiography

Transthoracic 2D echocardiographic examinations were performed within 48 hours after admission to our ICU and then every other day during the first week. A 5-MH transducer (Vivid S7, General Electric Medical System, Horten, Norway) was used. The following echocardiographic views were recorded: left parasternal long-axis views and apical long-axis two- and four-chamber views. Further, we recorded standard measurements of LV dimension and systolic function including LV volumes, left ventricular ejection fraction (LVEF) using a modified Simpson's rule, aortic annulus diameter in mid-

Table 1. Patient characteristics

Age (years)	58 (29-76)
Male gender, n (%)	24 (77)
Body mass index (kg/m^2)	32.0 ± 7.3
Body surface area (m^2)	2.1 ± 0.3
SAPS III score on ICU arrival	63 ± 11
Length of ICU stay (days)	19 (5-55)
ICU mortality, n (%)	6 (19)
30-day mortality, n (%)	3 (10)
Milrinone inhalation, n (%)	8 (26)
Previous medical history, n (%)	
Obesity	14 (45)
Hypertension	12 (39)
Lung disease	7 (23)
Diabetes mellitus	5 (16)
Cardiovascular disease	6 (19)
History of smoking	5 (16)
Immune deficiency	2 (6)
No comorbidities	9 (29)

Data are expressed as mean ± 1 SD or number (percentage). SAPS, simplified acute physiology score; ICU, intensive care unit.

systole (D), time velocity integral in the LV outflow tract (TVI-LVOT) from aortic Doppler flow profile and stroke volume (π x (D/2)^2 x TVI-LVOT) and cardiac index (SV* heart rate/body surface area). Finally, mitral Doppler flow profiles were recorded for measurements of peak early LV diastolic flow deceleration time (E deceleration time) and maximum flow velocity during LV early (E), late (A) diastolic filling E/A ratio [17].

Right ventricular measurements were obtained from a standard four-chamber view including end-diastolic RV area (RV EDA), end-systolic RV area (RV ESA) and RV basal diameter. Pulsed Doppler from RVOT, M-mode and tissue Doppler of the right ventricular free wall, continuous wave Doppler of the tricuspid regurgitant jet and respiratory collapsibility of the inferior vena cava were also recorded. Right ventricular systolic function was evaluated by variables as tricuspid annular plane systolic excursion (TAPSE), systolic tricuspid lateral annular velocity (S') and fractional area of change (FAC = (end-diastolic area-end-systolic are)/(end-diastolic area) *100). The hemodynamic right-sided assessment included measurements of the pulmonary flow acceleration time (AT) from the RVOT valve Doppler flow, tricuspid regurgitation pressure gradient (TVG) and estimation of systolic pulmonary arterial pressure (SPAP) by TVG and estimated central venous pressure (CVP). Strain measurements of LV were performed off-line in the four-chamber, long-axis and two-chamber views. All off-line analyses were performed using the EchoPAC workstation version 201 (GE Medical Systems, Milwaukee, Wisconsin, USA). From the analysis, we calculated the longitudinal strain of the free RV wall, as well as the global longitudinal strain (GLS) for the LVI. Myocardial strain (S) is presented as the fractional change (%) in length between two time points, end-diastole (L_0) and end-systole (L) and calculated as: $(L-L_0)/L_0 \times 100$. Negative values of strain indicate myocardial shortening. The overall RV dimension and function were evaluated using an RV score including six RV variables (cut-off values indicating RV dilation and dysfunction): RV EDA indexed to BSA (> 12 cm^2/m^2), FAC (< 35%), s' (< 9.5 cm/s), AT (< 100 ms), RV strain (> -20%) and SPAP (≥ 45 mm Hg), RV dysfunction was defined as an RV score of > 3 [17].

Statistics

Continuous variables were checked for normality. Normally distributed variables are presented as the mean ± standard deviation and non-normally distributed variables are presented as the median (interquartile range). A t-test was used to compare the means of right and left ventricular variables before and after inhalation of milrinone (**Table 5**). Mann-Whitney U test was used for comparisons biomarkers at the first echocardiographic examination in patients with low versus high right ventricular score (**Table 3**). Unadjusted correlations between biomarkers and echocardiographic parameters of patients' first measurements were examined and presented using Spearman's rank correlation coefficient. Spearman's correlation coefficients of the change in biomarkers and echocardiographic parameters are also presented. The change is calculated from the first to the last measurement for each patient. A probability level (*P*-value) of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS for Mac version 21.

Results

Thirty-one patients, 24 male and 7 females, with a median age of 58 years (range 29-76,

Table 2. Clinical, laboratory and echocardiographic data at the first echocardiographic examination

Time from ICU arrival (days)	1 (0-7)
Mechanical ventilation, n (%)	31 (100)
Vasopressor therapy, n (%)	31 (100)
Continuous renal replacement therapy, n (%)	4 (13)
Respiratory variables	
Positive end-expiratory pressure (mmHg)	14.4 ± 2.4
Tidal volume (ml)	490 ± 102
Respiratory rate (breaths per minute)	20 ± 4
Inspired fraction of oxygen (%)	52 ± 18
Hemodynamic variables	
Systolic arterial pressure (mmHg)	129 ± 20
Diastolic arterial pressure (mmHg)	66 ± 10
Heart rate (beats per minute)	86 ± 11
Arterial blood gas	
pH	7.36 ± 0.10
PaO_2 (kPa/mmHg)	10.4 ± 2.1/78 ± 16
$PaCO_2$ (kPa/mmHg)	5.9 ± 1.2 /45 ± 9
Lactate (mmol/L)	1.3 ± 0.4
Laboratory variables (median, interquarter range)	
Creatinine (μmol/L)	87 (64-209)
NT pro BNP (ng/l)	225 (164-642)
High-sensitive troponin-T (ng/l)	13 (9-21)
D-dimer (ng/ml)	1.2 (0.8-2.2)
Fibrinogen (g/l)	6.9 (6.2-8.8)
Echocardiographic data	
Right ventricular basal diameter (mm)	40.5 ± 4.7
Right ventricular end-diastolic area (cm^2)	26 ± 7
Right ventricular end-systolic area (cm^2)	15 ± 6
Right ventricular fractional area of change (%)	41 ± 10
Right ventricular free wall peak strain (-%)	22 ± 6
Tricuspid annular plane systolic excursion (TAPSE, mm)	21 ± 3
Systolic tricuspid lateral annular velocity (S', cm/s)	12 ± 3
Acceleration time right ventricular outflow tract (RVOT AT, ms)	96 ± 25
Transtricuspid peak gradient (mmHg)	28 ± 9
Left ventricuar global longitudinal strain (%)	17 ± 3
Time velocity integral of the LV outflow tract (TVI-LVOT, cm)	19 ± 4
Stroke volume (ml)	72 ± 19
Stroke volume index (ml/m^2)	34 ± 9
Cardiac output (l/min)	5.3 ± 1.7
Cardiac index ($l/min/m^2$)	2.5 ± 0.7
Left ventricular ejaction fraction (%)	54 ± 7

Data are expressed as mean ± 1 SD or number (percentage). Data with non-normal distrubution are expressed as median (range). Abbreviations: ICU, intensive care unit; NT pro BNP, N-terminal pro brain naturetic peptide; PaO_2, partial arterial pressure of oxygen; $PaCO_2$, partial arterial pressure of carbon dioxide.

Table 1), were included in the study. Most patients had their first echocardiographic examination within 48 hours after ICU arrival. Twenty-six patients had a second echocardiographic examination, while 16 patients had a third, 6 patients had a fourth and, finally, 2 patients had a fifth examination. The mean SAPS 3 score was 63 ± 11 and all the patients

Table 3. Biomarkers at the first echocardiographic examination in patients with low versus high right ventricular score

	RV-score 0-3	RV-score 4-6	*P*-value
hs TNT	9.6 (7.9-12.2)	22.5 (8.6-61.0)	0.057
NT-pro BNP	207 (110-311)	268 (188-2570)	0.064
d-Dimer	1.1 (0.5-1.6)	1.2 (1-2.6)	0.328
Fibrinogen	6.3 (6.0-7.3)	7.2 (6.7-9.0)	0.407

RV, right ventricular; hs TNT, high-sensitive troponin; NT-pro BNP, N terminal-pro brain natriuretic peptide.

needed mechanical ventilation and a norepinephrine infusion to maintain a MAP of > 65 mmHg. Further, 4 patients (13%) had continuous renal replacement therapy. The total ICU mortality was 19%, while the 30-day mortality was 10%. Pre-ICU comorbidities were present in 70% of the patients, with obesity being the most common, followed by hypertension and lung disease (**Table 1**). Clinical and laboratory data are shown in **Table 2**.

Echocardiographic parameters

Data on the echocardiographic variables are also shown in **Table 2**. The most common echocardiographic finding among the patients was RV dilation with or without systolic dysfunction. Right ventricular dilation, defined as a basal diastolic right ventricular diameter exceeding 4.1 cm and/or an RV end-diastolic area of > 25 cm^2, was found in 62% of the patients. Indices of RV systolic function, at the first examination, as FAC, RV strain and RV s', were abnormal in 30%, 31% and 53% of patients respectively. Pulmonary AT was shorter than the reference value of 100 msec in 55% and a TVG of > 35 mmHg was found in 24%, while an SPAP of > 45 mmHg was found in 38% of the initial echocardiograms. Twenty-two of 31 patients (70 %) had an RV score of 0-3 and 9 (30%) had an RV score of 4-6.

A cardiac index lower than 2.5 l/min*m^2 was initially found in 58% of the patients. An LVEF of < 50% and a GLS of < -16% were present in 10% and 16% respectively and the RV score in this group of patients was low, ranging between 1-3. The proportion of patients, however, with both an impaired LVEF and a reduced cardiac index at the first examination was 7%. Diastolic dysfunction with high filling pressures was not found in this group of patients and a deceleration time longer than 250 msec was only found in 2 of 31 (6%) patients.

Biomarkers and echocardiographic parameters

Overall, a considerable number of patients (42%) had abnormal hs-TNT levels (*i.e.* > 15 ng/l) on arrival at the ICU, while NT-proBNP was elevated in 8 (25%) patients. There were no associations between the levels of hs-TnT or NT-proBNP and RV function (**Table 3**). In patients with impaired LV function, the levels of hs-TNT ranged between 14.8 and 20.4 ng/l. The comparison of levels of biomarkers at the first examination between groups with a low RV score (0-3) versus a high RV score (4-6) did not reveal any statistically significant difference (**Table 3**).

In **Table 4**, the Spearman correlation coefficients between RV variables and biomarkers at the first examination are shown. Pulmonary flow AT, TVG and SPAP were significantly correlated to the levels of D-dimer but not to the levels of fibrinogen. The RV systolic variables as RV strain, TAPSE, s and RV score, as well as CI, LVEF and GLS, lacked any significant correlation to these biomarkers at the first examination. **Table 4** also shows the Spearman correlation coefficient of the change in the two variables. The change is calculated from the first to the final measurement for each patient. Even here, changes in the remaining variables of RV and LV function were not correlated to any changes in the levels of D-dimer or fibrinogen.

Milrinone inhalation

Right and left ventricular variables were compared before and after milrinone inhalation in the subgroup of patients (n=8, 26%) given this treatment. As shown in **Table 5**, milrinone affected neither indices of LV or RV function nor SPAP (Supplementary Figure 1).

Discussion

The rationale of this study was to evaluate the incidence of RV/LV impairment in critically ill patients with COVID-19 requiring mechanical ventilation. The main results were that RV dysfunction were commonly seen, while the incidence of LV dysfunction, as well as the inci-

Table 4. Spearman's correlation between biomarkers and echocardiographic variables

	First echocardiographic examination			The change of variables		
	d-dimer	Fibrinogen	hs TNT	d-dimer	Fibrinogen	hs TNT
FAC	-0.26 (0.184)	-0.16 (0.171)	-0.17 (0.301)	0.25 (0.353)	0.05 (0.841)	-0.12 (0.616)
RV-strain	-0.25 (0.178)	-0.01 (0.962)	-0.24 (0.197)	-0.37 (0.127)	0.45 (0.057)	-0.38 (0.061)
RV-diameter	0.09 (0.675)	0.17 (0.418)	0.39 (0.053)	0.11(0.660)	0.41 (0.084)	-0.17 (0.434)
AT	-0.54 (0.016)*	-0.19 (0.321)	-0.43 (0.017)*	-0.50 (0.030)*	-0.24 (0.309)	-0.19 (0.339)
TVG	0.52 (0.006)*	0.18 (0.389)	0.38 (0.050)	0.55 (0.021)*	-0.34 (0.194)	0.12 (0.612)
SPAP	0.63 (0.04)*	0.172 (0.496)	0.411 (0.46)	0.57 (0.017)*	-0.41 (0.111)	0.13 (0.591)
TAPSE	-0.17 (0.095)	0.07 (0.721)	-0.25 (0.186)	-0.17 (0.459)	-0.01 (0.979)	-0.21 (0.309)
Tricuspid s'	0.01 (0.973)	-0.24 (0.223)	-0.09 (0.604)	-0.13 (0.616)	0.21 (0.414)	-0.12 (0.579)

Data are presented as r (*P*-value) and * indicates significant correlation. AT, acceleration time of pulsed Doppler at right ventricular outflow tract; FAC, fractional area change; RV, right ventricular; SPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; Tricuspid s', systolic tricuspid lateral annular velocity; TVG, trans-tricupid valve gradient.

Table 5. Right and left ventricular variables before and after inhalation of milrinone

	Before milrinone inhalation	After milrinone inhalation	*P*-value
RV-strain (-%)	20.5 ± 3.7	23.2 ± 4.6	0.268
FAC (%)	36.2 ± 11.0	31.2 ± 7.4	0.127
TAPSE (cm)	1.9 ± 0.4	2.1 ± 0.5	0.265
RV s' (cm/s)	12.6 ± 1.1	12.8 ± 1.6	0.871
AT (ms)	78.4 ± 11.8	73.4 ± 13.4	0.381
RV-diameter (cm)	4.4 ± 0.7	4.1 ± 0.3	0.218
RVEDA index (cm^2/m^2)	12.3 ± 1.6	12.0 ± 2.5	0.652
TVG (mm Hg)	42.8 ± 7.6	41.5 ± 14.4	0.851
SPAP (mm Hg)	55.7 ± 10.1	52.4 ± 16.4	0.680
CI (L/m^2)	2.5 ± 0.4	2.8 ± 0.6	0.263
LVEF (%)	62.8 ± 8.2	55.0 ± 11.4	0.237
LV GLS (-%)	18.0 ± 2.6	18.8 ± 2.9	0.289

Data are presented as mean ± SD. Abbreviations as in **Table 4**. CI, cardiac index; LV, left ventricular; RVEDA index, right ventricular end-diastolic area indexed to body surface area; LVEF, Left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain.

dence of biventricular failure, were low. Variables reflecting RV afterload, such as pulmonary flow AT, TVG and SPAP, correlated well to D-dimer levels. These results, in combination with the fact that milrinone inhalation did not have any significant impact on RV systolic function or afterload, argue against an increase in RV afterload due to profound hypoxic vasoconstriction and support the hypothesis of thrombosis/pulmonary embolism as the main cause of increased RV afterload in these patients.

In the present study, the incidence of impaired LV dysfunction was low and none of our patients had LV diastolic dysfunction with high filling pressures. The RV score was also low, in patients with impaired LV systolic function, ranging between 1-3, while the levels of hs-TNT ranged between 14.8 and 20.4 ng/l. Recently, studies evaluating heart function in patients with COVID-19, using both echocardiography and cardiac biomarkers, have resulted in the belief held by some researchers that the COVID-19 infection has a direct myocardial involvement presented as myopericarditis [20]. while others suggest that heart dysfunction is caused by an RV overload and/-or RV systolic dysfunction *per se* caused by acute lung damage [16, 18]. The hypothesis of a COVID-19-induced injury to the myocardium has been supported mainly by the elevated levels of troponins and natriuretic peptides [1, 7]. Obviously, our data are unable to support the hypothesis of major myocardial damage with biventricular involvement. However, this conclusion may have limited value, as only 3 in 31 patients had reduced EF of 38-45% and 5 had a reduced GLS of < -16%. Further, all patients were treated with a norepinephrine infusion during the time of examination, which could theoretically have concealed a reduced LVEF or GLS due to the β_1-mediated inotropic effect of norepinephrine.

In contrast to the LV function, RV dysfunction was commonly detected in our COVID-19 patients. Right ventricular dilation was the most commonly found, followed by an increased

RV afterload and impaired RV systolic dysfunction. In ARDS, as it is known RV dilation and/or failure is caused by a sudden increase in RV afterload and many conditions in the ICU may contribute to this. These conditions include mechanical ventilation with excessive PEEP, hypercarbia, hypoxic pulmonary vasoconstriction and pulmonary embolism. In a recently published study on cardiac manifestation in COVID-19 [16], RV dilation was common and often associated with a shortened AT. These patients had worse lung disease, lower oxygen saturation, higher LV filling pressure and inflammation biomarkers, suggesting that the etiology for elevated RV afterload in COVID-19 is multifactorial. In our study, all the patients had mechanical ventilation with a PEEP averaging 14.4 ± 2.4 mmHg. We actively tried to avoid both severe hypoxia and hypercarbia by utilizing the prone position as well as a continous optimization of ventilator settings. However, we can not exclude that the positive pressure ventilation could partly explain the elevated RV afterload and that hypoxic vasoconstriction due to profound lung damage could lead to increased pulmonary vascular resistance.

Furthermore, recent studies have demonstrated that COVID-19 patients often present with high levels of D-dimer, fibrinogen, thrombosis and angiogenesis in the pulmonary vascular bed [19-21]. Our data support the presence of pulmonary thrombosis/embolism as all RV-afterload variables correlated significantly to D-dimer. This hypothesis is also reinforced by the fact that CT angiography in three patients with RV dilation and high pulmonary arterial pressure revealed pulmonary embolism. Unfortunately, CT angiography was not performed in the rest of the study group. The correlation of RV-afterload variables to the levels of fibrinogen was not significant, a notion that can be explained by the fact that fibrinogen is a biomarker of acute inflammation rather than of coagulopathy [22].

Our data are in line with a recently published study on cardiac manifestation in COVID-19 [16]. It found that RV dilation was common and often associated with a shortened AT. Patients with a shorter AT had worse lung disease, lower oxygen saturation, higher LV filling pressure and inflammation biomarkers, suggesting that the reason for the elevated RV afterload in COVID-19 is multifactorial. In our study, all the patients had mechanical ventilation with a PEEP averaging 14.4 ± 2.4 mmHg. The positive pressure ventilation could partly explain the elevated RV afterload, but hypoxic vasoconstriction due to profound lung damage could lead to increased pulmonary vascular resistance, even though we attempted to avoid hypercarbia and hypoxemia by using mechanical ventilation and the prone position.

In the present study, 8 patients received milrinone inhalations indicated by a clinical deterioration, *i.e,* an SPAP of > 60 mmHg and an FiO_2 of > 60% in spite of a prone position. It has previously been shown that the inhalation of aerosolized milrinone causes selective pulmonary vasodilation in patients with pulmonary hypertension after cardiac surgery [23]. Furthermore, the inhalation of milrinone prevents pulmonary endothelial dysfunction and vasoconstriction in patients undergoing cardiac bypass [24]. We monitored the effects of milrinone with echocardiography at least 24 hours after the start of treatment. However, we were unable to demonstrate any clinical improvement or change in either RV function or afterload variables using inhaled milrinone in COVID-19 patients with high SPAP, arguing for thrombo-embolism being the main cause of the RV changes that were found.

Limitations

The main limitation in the present study was the small number of included patients. Another limitation was that fibrinogen and D-dimer were only analyzed once weekly and not daily. Further, due to the heavy workload, we failed to measure central venous pressure (CVP) invasively in all patients. Instead, we estimated CVP by visualizing the vena cava inferior with echocardiography. In addition, we only included 8 patients for the evaluation of inhaled milrinone on RV afterload and performance. Finally, we did not insert a pulmonary artery catheter for the assessment of pulmonary vascular resistance. The main strengths of this study were its homogeneity, comprising a group of critically ill COVID-19 ICU-patients, all hemodynamically compromised and requiring mechanical ventilation and a norepinephrine infusion, and the fact that we evaluated a treatment for selective pulmonary vasodilation on RV afterload and function.

Conclusions

In this prospective, observational echocardiographic study of intubated ICU patients with COVID-19, we found a high frequency of RV dilation and dysfunction. Further, we found no association between cardiac biomarkers and LV or RV function assessed by echocardiography. However, indices of RV afterload correlated well to D-dimer levels. Selective pulmonary vasodilation using an inhalation of milrinone was unble to improve RV function or afterload, suggesting that the main reason for the increase in RV afterload was speculatively pulmonary thrombosis/embolism rather than hypoxic vasoconstriction.

Disclosure of conflict of interest

None.

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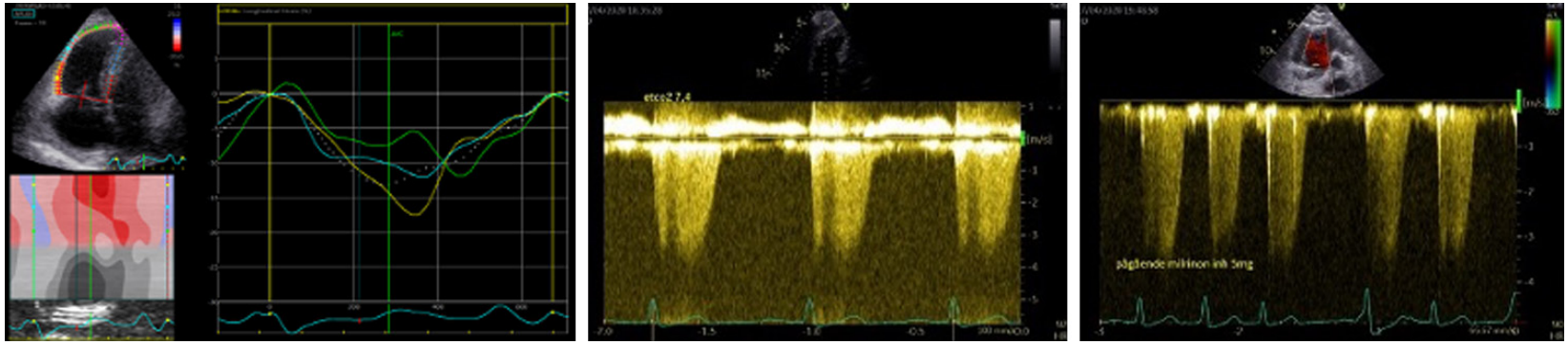

Supplementary Figure 1. Shows the RV-dilatation and impaired RV free wall strain in a COVID-19/ICU patient and the differences between tricuspid valve gradients (TVG) before and 24 hours after the initiation of inhalations of milrinone.