Research paper

Coupling of right ventricular function to pulmonary circulation as an independent predictor for non invasive ventilation failure in SARSCoV 2-related acute respiratory distress syndrome

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ABSTRACT

Study objectives: To assess whether echocardiography, systematically performed, could help in risk stratifying patients with acute respiratory distress syndrome (ARDS) due to SARS-CoV2 (COVID) infection for non invasive ventilation (NIV) failure.
Design: Observational single center investigation.
Setting: Intensive care unit.
Interventions: Echocardiography.
Outcome measures: NIV failure.
Main results: Seventy-five patients were included in our study. In respect to patients who did not need mechanical ventilation (NIV success), those in the NIV failure subgroup (31 patients, 41 %) were older, with more comorbidities and showed a higher SOFA score and LOS. Higher values of NTpro BNP, CRP and D-dimer were observed in the NIV failure subgroup who exhibited a higher ICU mortality rate. At echocardiographic examination, the NIV failure subgroup showed higher values of RV/LV ratio, systolic pulmonary arterial pressure (sPAP) and lower values of tricuspid annular plane systolic excursion (TAPSE)/SPAP, and PaO2/FiO2. At logistic regression analysis TAPSE/sPAP resulted an independent predictor of NIV failure. At receiving operating characteristic curve analysis, the TAPSE/SPAP cut-off of 0.575 mm/mm Hg showed a sensitivity of 97 % and a specificity of 48 %.
Conclusions: Our results documented a marked uncoupling of right ventricular function from the pulmonary circulation (as indicated by TAPSE/sPAP) in COVID-related ARDS treated with non invasive ventilation and the measurement of this parameter, performed on ICU admission, provides independent prognostic relevance for NIV failure.

1. Introduction

Non invasive ventilation (NIV) has been widely used in patients with SARS-CoV2 (COVID) related acute respiratory distress syndrome (ARDS), with different rates of success, probably due to disparate hospital policies and availability of healthcare resources [1,2]. Recently, PO2/FiO2 ratio measured after 24 h since NIV start and its change from baseline were significantly associated with NIV success at univariate analysis in a small population of 30 patients [3]. The timely identification of patients at higher risk of NIV failure (that is need of mechanical ventilation) has both a clinical and an organizational impact, though data on this topic are so far scarce [1–3]. Echocardiography has emerged as a clinical tool in managing and risk stratifying patients with COVID-related ARDS and, in particular right ventricular (RV) dilatation and dysfunction proved to be predictors of adverse outcome in these patients [4–7]. We evaluated whether echocardiography, systematically performed, could help in this risk stratification process, focusing on the coupling of right ventricular function to the pulmonary circulation, as indicated by tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary artery pressure (PASP) ratio [8,9].

2. Methods

In our retrospective case series we enrolled all patients with COVID-

related severe respiratory failure treated with NIV, consecutively admitted to our intensive care unit (ICU) (1st April 2020–1st March 2021) which is an ECMO referral center. The study protocol was approved by our Ethical Committee ("Comitato Etico Area Vasta Centro", approved on March 31th 2020, n.17024). Our hospital (Azienda-Ospedaliera Universitarya Careggi) is a teaching hospital.

The written inform consent for each patient was waived for emerging infectious disease. Every day relatives were informed by phone on the clinical conditions of their kin.

NIV was performed using full-face mask. The size of the mask was adapted to the patient's face and neck, as well the fixing system. The mask size and fitting were closely supervised to minimize leaks as much as possible. Positive end expiratory pressure (PEEP) was initially set at 8 cmH2O and subsequently fine-tuned according to clinical parameters. Pressure support (PS) was set at 10 cmH2O, and then progressively modified, according to tidal volume and respiratory drive.

Echocardiography was performed as previously described [4,6], on ICU admission (within 12 h) in each patient, during NIV treatment.

The right ventricle size is assessed by the RV end-diastolic area (EDA) and the ratio between EDAs of the right and left ventricles was calculated (RVEDA/LVEDA).

Systolic pulmonary artery pressure (sPAP) is obtained using the simplified Bernouilli's equation: $4 \cdot$ (Vmax tricuspid regurgitation − Doppler technique)2 + central venous pressure (CVP). All patients had their CVP measured through a central venous line. Each measure is performed three times, and the mean value was recorded. Tricuspid Annular Plane Excursion (TAPSE) is also measured, as the difference of displacement during diastole and systole. RV dilatation and dysfunction (RVDys) was defined in presence of RVEDA/LVEDA > 0.6 and TAPSE < 15 mm.

Coupling of right ventricular function to the pulmonary circulation was evaluated as the tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary artery pressure (PASP) ratio [8–10].

All ultrasound cardiac procedures are performed using the necessary protective equipment for professionals. Dedicate machines are used in the COVID ICU and transducers are wrapped in single-use plastic covers [4,6,11]. All measurements taken for each examination were averaged over a minimum of three cardiac cycles (five to ten in case of non-sinus rhythm).

Primary outcome was the need for mechanical ventilation (NIV failure).

2.1. Statistical analysis

Data have been stored in a dedicated data-base and analyzed with SPSS for Windows 20.0 (SPSS Inc., Chicago, IL). p value <0.05 was considered statistically significant. Categorical variables are reported as frequencies and percentages, continuous as mean ± standard deviation (SD) or median (interquartile range, IQR), as needed. Between groups comparisons are performed by means of chi-square (categorical data) or, for continuous data, with Student's t-test and/or Kruskal-Wallis test, as appropriate. Logistic regression models are developed to detect predictor(s) for NIV failure. The three patients who had a DNI code were not included in the comparison of echocardiographic data and in the logistic regression analysis. Considering the low number of events (number of patients who experienced NIV failure), a limited number of covariates were entered in the multivariable model (to avoid overfitting) and two different models were calculated. The following variables were considered: age and TAPSE/sPAP (Model 1) and D-dimer and SOFA (Model 2). Receiving operating characteristic curve is constructed to identify the cut-off for TAPSE/SPAP in relation to NIV failure.

3. Results

Our series comprises 75 consecutive patients treated with NIV, among whom 31 patients (41 %) needed mechanical ventilation (NIV

failure subgroup) and 44 patients did not (NIV success) (Table 1). When compared with NIV success subgroup, patients in the NIV failure subgroup were older, with more comorbidities and showed a higher SOFA score.

Higher values of NT-pro BNP, C-reactive protein (CRP) and D-dimer were observed in the NIV failure subgroup who exhibited a higher length of stay (NIV failure: 13 ± 9 vs NIV success: 8 ± 5 days, p = 0.02) and ICU mortality rate (NIV failure: 19 (61 %) vs NIV success: 4 (9 %), p = 0.001).

The overall mortality rate was 31 % (23/75). Among the NIV success subgroup, one patient (aged 82) died because of acute myocardial infarction complicated by cardiac arrest and three patients (aged 85, 89 and 90, respectively) had a DNI code. At echocardiography, the NIV failure subgroup showed higher values of RVEDA/LVEDA ratio, sPAP and lower values of TAPSE/SPAP, and PaO2/FiO2 (Table 1). No patient included in our study had pulmonary valve stenosis. Tricuspid regurgitation was moderate in 42 patients (66 %) and severe in 33 patients (44 %).

Pulmonary embolism was detected at CT scan in 8 patients (10 %) among whom 5 patients were in the NIV failure group.

At logistic regression analysis (Table 2) the following parameters resulted independent predictors of NIV failure: age (OR 1.0642; 95 % CI 1.012–1.118; p = 0.0154) and TAPSE/SPAP (OR 0.0464; 95 % CI 0.225–0.943; p = 0.033) (Model 1) and D-dimer (OR 1.051; 95 % CI 1.0021–1.100; p = 0.044), when adjusted for SOFA (OR 1.033; 95 % CI 0.944–1.129; p = 0.510) (Model 2).

At receiving operating characteristic curve analysis, the TAPSE/SPAP cut-off of 0.575 mm/mm Hg showed a sensitivity of 97 % and a specificity of 48 %. Area under the curve was 0.751 (95 % CI 0.641–0.862); p < 0.001 (Fig. 1).

Table 1
Baseline characteristics of patients.

Parameter	NIV failure	NIV success	p value
Number	31 (41 %)	44 (59 %)	
Age (years, mean ± SD)	70 ± 13	60 ± 13	0.012
Gender (n, %)	24 (72 %)	32 (72 %)	0.988 (chi square)
BMI (mean ± SD)	30 ± 9	28 ± 4	0.528
Charlson's index (mean ± SD)	4.5 ± 3	2.6 ± 2	0.014
Time from symptoms' onset (days) (mean ± SD)	6 ± 5	5.5 ± 8	0.923
SOFA median (IQR)	6 (3–8)	2 (1–3.5)	<0.001
Biohumoral data			
Creatinine (mg/dl) (mean ± SD)	1.31 ± 1	0.8 ± 1	0.09
Troponin (pg/ml), median (IQR)	7.5 (20–37)	7.25 (14–49)	0.779
NT-proBNP (pg/ml), median (IQR)	1155 (396–2364)	221 (105–1232)	0.008
CRP (mg/dl), median (IQR)	138 (96.5–180)	49 (22–163)	0.04
D-dimer (ng/ml), median (IQR)	1950 (978–3738)	926 (713–1525)	0.016
Echocardiographic data			
LVEF (%) (mean ± SD)	58 ± 9	60 ± 10	0.377
RV/LV (mean ± SD)	0.43 ± 0.07	0.39 ± 0.05	0.008
TAPSE (mm) (mean ± SD)	22 ± 1	21 ± 1	0.982
SPAP (mm Hg) median (IQR)	41.5 (22–55)	40 (38–45)	0.003
TAPSE/SPAP (mean ± SD)	0.450 ± 0.099	0.542 ± 0.105	<0.001
P/F median (IQR)	81.5 (66–103)	123–5 (110–145)	0.049

BMI: body mass index, ICU: intensive care unit, LOS: length of stay, CRP: C-reactive protein, SOFA: simplified organ functional assessment, NT-pro BNP: N terminal pro brain natriuretic peptide, LVEF: left ventricular ejection fraction, TAPSE: tricuspid annular plane systolic excursion, sPAP: systolic pulmonary arterial pressure, P/F: PaO2/FiO2 ratio, SD: standard deviation, IQR: interquartile range, (t): Student t-test, KW: Kruskal-Wallis test,

Table 2
Logistic regression analysis.

	OR	95 % CI	p
Model 1			
Age	1.064	1.012–1.119	p = 0.015
TAPSE/SPAP	0.0463	0.227–0.943	p = 0.034
Model 2			
D-dimer	1.050	1.002–1.100	p = 0.043
SOFA	1.03	0.942–1.129	p = 0.508

OR: odd ratio, CI: confidence interval, TAPSE/SPAP: tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure, SOFA: sequential organ failure assessment.
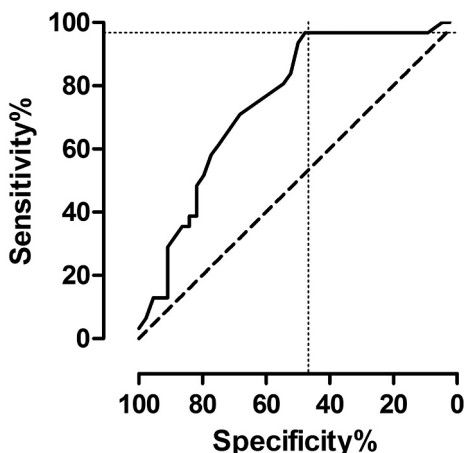

Fig. 1. ROC analysis.

4. Discussion

Our data suggest that echocardiography may be helpful in risk stratification of patients with COVID-related ARDS on NIV since coupling of ventricular function to pulmonary circulation (as indicated by TAPSE/sPAP ratio) was an independent predictor of NIV failure (Table 2).

In our series, the percentage of NIV failure was comparable with that reported by Bellani et al. [12] who observed, in 909 patients treated outside the ICU, an overall success rate of NIV (predominantly helmet cPAP) of 65 %. On the contrary in a large retrospective cohort [13], among the 747 patients requiring NIV, 572 patients (76.6 %) experienced NIV failure. Discrepancies among investigations come most likely from different hospital policies and utilization of healthcare resources, as well as from different pandemic periods. In a nationwide cohort of 17,023 COVID patients in Germany, utilization of NIV was described to significantly increase during the autumn period, with an increasing percentage of those failing NIV (from 9 % to 23 %). Mortality progressively increased from those who used NIV only to those who needed mechanical ventilation after a longer (>4 days) period of NIV (from 44 % to 72 %, respectively) [14].

The identification of predictors for NIV failure may have both clinical significance and organizational significance since, in the context of pandemic and overwhelmed hospitals, it may allow a tailored therapy in the single patient (early mechanical ventilation) and a more efficacious utilization of healthcare resource (early transfer to ICU) since the Emergency Department.

The novelty of the present investigation is that echocardiography, systematically performed, helped in this stratification process since the TAPSE/SPAP ratio, that is relationship between TAPSE (longitudinal RV fiber shortening) and sPAP (force generated by the RV) resulted an independent predictor of NIV failure.

This parameter is based on the concept that RV is particularly sensitive of pressure overload and that the combined assessment of longitudinal RV fiber shortening and pulmonary arterial pressures would provide more physiologic-based information and may improve risk stratification. This proved to be true in heart failure as well as in pulmonary arterial hypertension [8]. The TAPSE/sPAP was recently investigated [10] in 92 patients with COVID-related acute respiratory failure, among whom the majority (64 %) needed ventilatory support (22 patients on NIV and 37 on mechanical ventilation). In this heterogeneous population TAPSE/SPAP was an independent predictor of death with a calculated cutoff of 0.635 mm/mm Hg. We extend these findings in a more selected series (only in patients on NIV), though the two populations in these two studies (that by D'Alto [10] and ours) differs in disease severity (mortality rate 25 % [10] versus 31 % [ours]) and in treatment (ventilatory support in 64 % [10] and in all patients in our study).

Our results documented a marked uncoupling of right ventricular function from the pulmonary circulation (as indicated by TAPSE/sPAP) in COVID-related ARDS treated with non invasive ventilation and the measurement of this parameter by a comprehensive transthoracic echocardiography, performed on ICU admission provides independent prognostic relevance for NIV failure. In COVID disease, a progressive RV dilatation and dysfunction and increase in systolic pulmonary arterial pressure were described as lung disease worsens.

The combined assessment of RV myocardial length-tension relationship may better reflect the heart-lung interaction in COVID lung disease since this condition shows a peculiar fibrotic and prothrombotic phenotype mainly involving pulmonary vasculature and thus directly affecting RV chamber.

The strength of our investigation is the systematic use of echocardiography in all patients with COVID-related respiratory failure treated with NIV which allowed the detection of uncoupling between RV and pulmonary circulation in these patients.

A possible limitation of the present study is the limited number of patients. However, the use of echocardiography was systematic, with no bias of inclusion and patients were treated by the same medical team. However, since COVID treatment protocols evolve and medical teams treating COVID develop experience with time, the possibility that critical care did not change with time cannot be ruled out. Another possible limitation may be represented by the fact that we did not collect data on previous history of pulmonary hypertension or RV failure. Further studies are however needed to confirm our findings in larger cohorts.

5. Conclusions

Our results documented a marked uncoupling of the right ventricular function from the pulmonary circulation (as indicated by TAPSE/sPAP) in COVID related respiratory failure treated with non invasive ventilation and the measurement of this parameter, performed on ICU admission, provides independent prognostic relevance for NIV failure.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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