DOI: 10.1002/pul2.12179

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Pressure-based beat-to-beat right ventricular ejection fraction and Tau from continuous measured ventricular pressures in COVID-19 ARDS patients

Matthias Gaertner[1] | **Raymond Glocker**[2] | **Felix Glocker**[2] | **Hans-Bernd Hopf**[2,3]

[1]Department of Anesthesiology, Düsseldorf University Hospital, Düsseldorf, Germany

[2]emka MEDICAL GmbH, Aschaffenburg, Germany

[3]Department of Anaesthesia, Perioperative Medicine and Interdisciplinary Intensive Care Medicine, ECLS-ECMO Center Langen, Asklepios Klinik Langen, Langen, Germany

Correspondence
Matthias Gaertner, Department of Anesthesiology, Düsseldorf University Hospital, Moorenstrasse 5, 40225 Düsseldorf, Germany.
Email: Matthias.gaertner@med.uni-duesseldorf.de

Funding information
None

Abstract

We evaluated pressure-based right ventricular ejection fraction (RVEF) and diastolic isovolumetric relaxation time constant (Tau) from continuously (up to 30 days) invasive measured right ventricular pressures in mechanically ventilated patients with severe COVID-19 acute respiratory distress syndrome (ARDS). We retrospectively calculated beat-to-beat ejection fraction from right ventricular pressures and dp/dt maximum and minimum in 39 patients treated between October 1st, 2020 and June 30th, 2021. After performing a stepwise logistic regression with survival as a dependent variable, we divided the patients into survivors and nonsurvivors based on their 60-day mortality. Independent outcome variables were the values of RVEF and Tau over time after insertion of the right ventricular probe along with right ventricular systolic and diastolic pressures (RVSP) and the estimated pulmonary artery diastolic pressure (ePAD). RVEF increased significantly over time in the survivors (estimate: 0.354; 95% confidence interval, CI: 0.18–0.53; $p < 0.001$) but remained unchanged in the nonsurvivors. Tau increased significantly in the nonsurvivors (estimate: 0.001; 95% CI: 0.0004–0.0018; $p < 0.002$) but not in the survivors. On the last measurement day, RVSP and ePAD were significantly lower while RVEF was significantly higher in the survivors compared to the nonsurvivors. In COVID-19 ARDS patient's, calculation of beat-to-beat RVEF and Tau from continuously invasive measured right ventricular pressures seems to unravel contrary trends in RVEF with an increase in the surviving and a decrease in the nonsurviving patients. Tau remained unchanged in the surviving but increased in the nonsurviving patients over time.

KEYWORDS
ePAD, pulmonary hypertension, pulmonary vasodilators, RVEF, Tau

INTRODUCTION

Available data suggest that in patients with COVID-19 acute respiratory distress syndrome (ARDS) development of pulmonary hypertension (PH) in combination with right ventricular hypertension might be one of the key features associated with a worse prognosis.[1–3] In addition, right ventricular dysfunction seemed to be a major determinant of mortality in patients with COVID-19-induced lung injury.[4,5] We have recently shown, that in patients with COVID-19 ARDS right ventricular systolic pressures were substantial and significantly higher on the first day as well on the last day of our long-term measurements in the nonsurvivors compared to the survivors. Following the administration of pulmonary vasodilators, we also found a significant decrease in right ventricular systolic pressure (RVSP) over time in the survivors but not in the nonsurvivors.[6] In the present paper, we have used our final patient database of 39 mechanically ventilated patients with severe ARDS caused by COVID-19 pneumonia to calculate the right ventricular ejection fraction (RVEF) as well as the time constant Tau of the right ventricular isovolumetric relaxation time Tau from the continuous invasive measured right ventricular pressure curves using a modification of the recently published single-beat approaches for the calculation of RVEF[7,8] and Tau.[9,10]

METHODS

Patient selection

With the approval of the local ethic committee (LAEK Hessen 2021-2415-evBO), we retrospectively evaluated 39 invasively ventilated patients with severe COVID-19 ARDS confirmed by a positive polymerase chain reaction test and a native or contrast media enforced thoracic computed tomography (CT) scan showing COVID-19 typical opacified pulmonary infiltrations in whom a right ventricular pressure probe for continuous long-term right ventricular pressure measurement has been inserted between October 1st, 2020 and June 17th, 2021. In all patients, informed consent of the patient or their next relative was obtained before the insertion of the catheter. In 32/39 patients venovenous extracorporeal membrane oxygenation (ECMO) has been instituted along the guidelines as described previously by Combes et al.[11] Standard ECMO settings were 3000–3500 rpm to generate a flow between 3.5 and 4.5 lpm to achieve a partial pressure of oxygen (paO_2) >60 mmHg and a sweep-flow to achieve a partial pressure of carbon dioxide <60 mmHg with a pH >7.30. All patients breathed spontaneously in the pressure assist mode with the positive end-expiratory pressures adjusted according to either repetitive daily measurements of functional residual capacity by the intensive care unit (ICU) ventilator (Carestation™; General Electric) or to clinical improvement along with an increase in the paO_2/fraction of inspired oxygen ratio above 100 mmHg. The applied positive end-expiratory pressures (PEEP) ranged from 7 to 15 cmH_2O, the applied driving pressure ranged from 7 to a maximum of 15 cmH_2O. With exception of a continuous infusion of sufentanil, no sedatives were used. If clinically indicated, clonidine or dexmedetomidine was added to achieve a Richmond agitation sedation scale of −1 to 0.

CorLog probe implantation and functions

In all patients the CorLog system® (emka medical GmbH) composed of CorLog Probe, CorLog connect, and CorLog application software (App, CE-0482 mark on April 7, 2021) was used. Briefly, CorLog Probe 1P is a high-fidelity pressure measurement system designed for long-term (up to 30 days) use in the right atrium or the right ventricle (40 or 35 cm long) using Fluorinert® fluid as transmission fluid. The probe (outer diameter: 3F) is inserted transcutaneously via the internal jugular or the subclavian vein. The use in our patients was permitted by annex XIII of the medical device regulatory of the European Union (custom-made devices, unmet clinical need), EU regulation 2017/745 of the European Parliament, and the European Council of April 5th, 2017.

The right ventricular pressure probe was inserted percutaneously under aseptic conditions via the left or right subclavian vein with a 6F split introducer cannula under local infiltration analgesia. The placement of the probe was guided by continuous pressure measurement while advancing the probe until typical right ventricular pressure curves could be recorded. After the removal of the split cannula, the probe was fixated at the insertion site with a purge string and the housing of the probe was fixated at the skin with four sutures. In each patient, the distance between the tip of the probe in the right ventricle and the sensor in the housing chamber was calculated based on the weight of the patient and the specific weight of the transmission fluid of the probe (1855 g/cm^3), that is, starting with 50 kg and 5.6 cm and 7.9 mmHg we add for each 10 kg in body weight 1 cm and 1.36 mmHg. Thus, after adjustment of the offset, the probe correctly measured real-time intracardial pressures with 30 days in vitro stability of 0.5 mmHg.[6] Transmission of continuous pressure recordings to the ICU bedside monitor and to a standard smartphone equipped

with the CorLog application software (App) via an interface (CorLog Connect) as well as storage and transfer of all recorded data for off-line analysis also have been described in detail previously.[6]

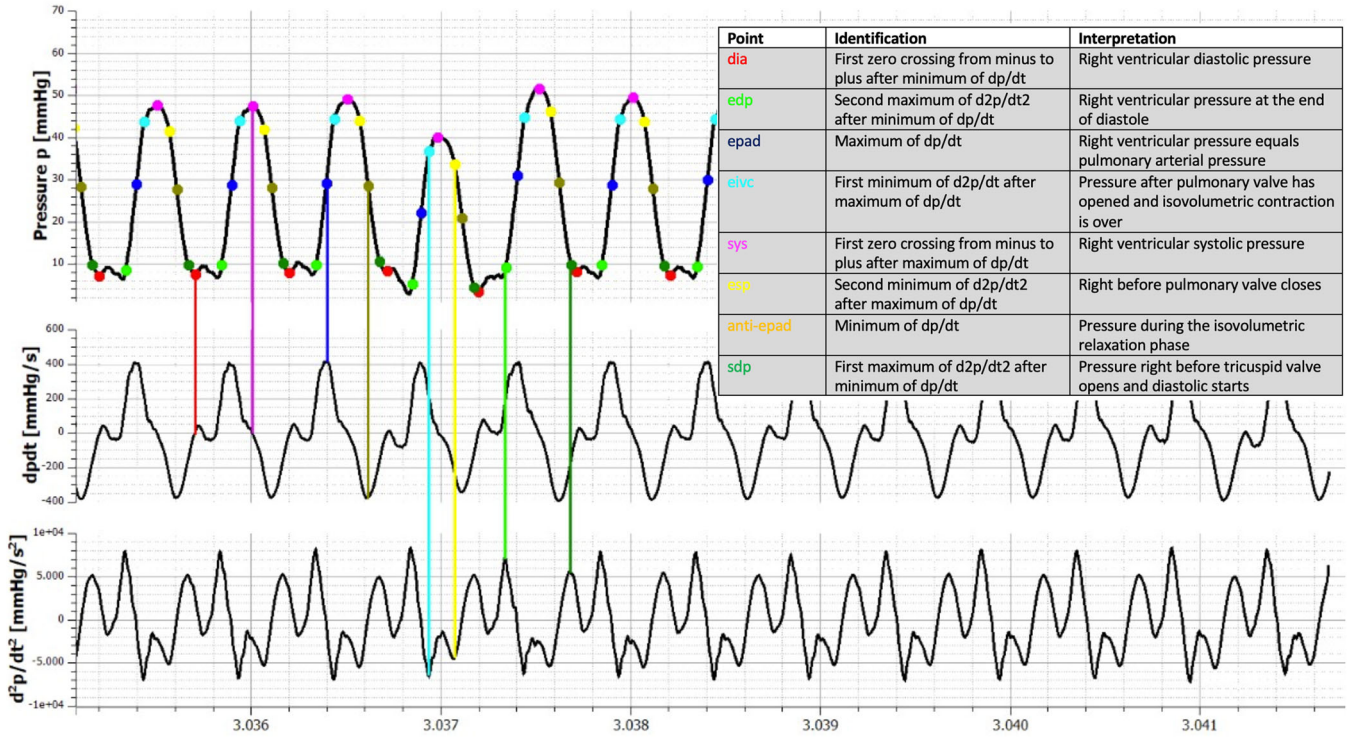
Identification of pressure points on the right ventricular pressure tracing

Using the first and second derivate of the right ventricular pressure with regard to time we identified eight distinct pressures as described previously.[12,13] A typical recording incorporating all eight pressure points is shown in Figure 1. These points build the basis for the calculation of the derived parameters.

Calculation of RVEF and Tau

Calculation of RVEF from pressure values only was first described by Heerdt et al.[7] The equation used is $\mathrm{RVEF} = 1 - \mathrm{esp}/P_{\max}$, where esp is the end-systolic pressure and $P_{\max}$ is the theoretically achieved pressure of the right ventricle if the isovolumetric contraction phase is interpolated to its maximum (=before the opening of the pulmonary valve). Several methods have been proposed for the calculation of $P_{\max}$ where the most used one is the regression of a sinus curve to the isovolumetric contraction and relaxation phase of the right ventricular pressure curve.[13–16] Recently Heerdt et al.[7,8] proposed the use of a Weibull function instead of a sinus function.

The method we used for the calculation of Pmax was proposed by Shih et al.[15] and calculates the crossing point of two tangents at the rising and falling part of the right ventricular pressure curve. The calculated crossing point, which we will call CROSS, is then transformed to the maximum value of the corresponding sinus function. Shih et al.[15] derived the following equation for this transformation: $P_{\max} = 2 \times (\mathrm{CROSS\text{-}A})/\mathrm{pi} + \text{“A,”}$ where “A” is (epad + anti-epad)/2. On the rising and falling part of the right ventricular pressure curve, a group of points was selected by using estimated pulmonary artery diastolic (epad) pressure and anti-epad and ±20% of measurements around these points. The tangents were constructed by linear regression through these measurements. We modified this approach by first using only two points for each tangent which were specified as epad −3



Point	Identification	Interpretation
dia	First zero crossing from minus to plus after minimum of dp/dt	Right ventricular diastolic pressure
edp	Second maximum of d2p/dt2 after minimum of dp/dt	Right ventricular pressure at the end of diastole
epad	Maximum of dp/dt	Right ventricular pressure equals pulmonary arterial pressure
eivc	First minimum of d2p/dt after maximum of dp/dt	Pressure after pulmonary valve has opened and isovolumetric contraction is over
sys	First zero crossing from minus to plus after maximum of dp/dt	Right ventricular systolic pressure
esp	Second minimum of d2p/dt2 after maximum of dp/dt	Right before pulmonary valve closes
anti-epad	Minimum of dp/dt	Pressure during the isovolumetric relaxation phase
sdp	First maximum of d2p/dt2 after minimum of dp/dt	Pressure right before tricuspid valve opens and diastolic starts

FIGURE 1 A typical example of a right ventricular pressure recording incorporating all identifiable measurement points necessary for the interpretation. Upper panel: Tracing of the right ventricular pressure, middle panel: first derivative of right ventricular pressure over time, and lower panel: second derivative of right ventricular pressure over time. Inlay in right upper corner: description of each detection point with the corresponding lines on the graphs of dp/dt and d2p/dt2 and the physiological interpretation (first, second, and third column of the inlay, respectively).

points and anti-epad +3 points with each point being 4 ms apart (Figure 2). Second, because the inflection points of a sinus curve have the same height on up- and downstroke but usually do not have the same height on up- and downstroke of the right ventricular pressure curve only epad was used for "A" instead of the mean of epad and anti-epad. This means the upstroke inflection point of the fitted sinus function coincidences with epad.

We compared our approach with the original method of Shih in 10 beats of four patients, respectively, with right ventricular pressures ranging from 35 to 60 mmHg and found an interindividual difference between both methods ranging from 1% to 3%.

For Tau, we used the logistic Tau as described by Ogilvie et al.[10] which can be calculated by the equation Tau = −(anti-epad – dia)/(2 × dpdt_min).

After extracting the data from each smartphone all original right ventricular tracings were checked visually by Hans-Bernd Hopf, Felix Glocker, and Raymond Glocker. for plausibility and accuracy. Thereafter, in each patient on each day where the probe was in place, the records of the 1-h period from 7:00 to 8:00, 15:00 to 16:00, and 23:00 to 00:00 were evaluated. In the case of missing values at these time points, the evaluation algorithm used a 1-h period either of the 2 h before or after the missing time point. The median value and range as well as the mean value and standard deviation of the periods described were calculated and again checked for accuracy and plausibility. Thereafter median and mean values of all patients both were stored in an excel spreadsheet for statistical analysis.

For each patient biometrical and comorbidity data as well as simplified acute physiology score 2 and sequential organ failure assessment scores at the start of mechanical ventilation therapy were recorded. Also, for each patient start and end as well as the dosage of pulmonary artery vasodilators (oral sildenafil and/or inhaled iloprost and/or inhaled nitric oxide) was recorded. Duration of noninvasive and invasive ventilation as well as the duration of the ECMO were also drafted from the patient's records and stored in the excel spreadsheet. The presence of pulmonary artery embolism as revealed by single or repetitive contrast media-enforced thoracic CT scans were also recorded.

Statistical methods

A logistic regression of all pressure variables of the whole group of 39 patients with survival as the dependent variable was performed. The regression was carried out stepwise backward. After evaluation of these data, we used 60-day mortality to separate the patients into two groups: survivors (Group 1, $n = 25$) and nonsurvivors (Group 2, $n = 14$). Independent outcome variables were the values of RVEF and the time constant Tau of the right ventricular diastolic isovolumetric relaxation time after insertion of the right ventricular probe as well

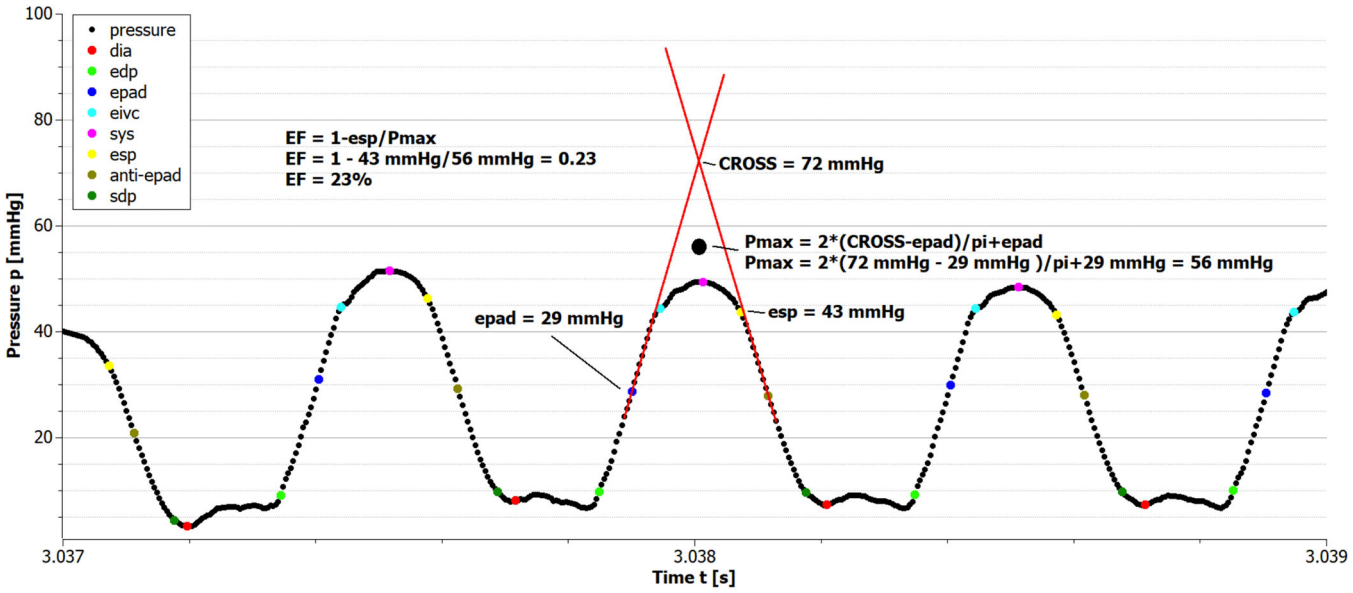


FIGURE 2 Calculation of right ventricular ejection fraction (RVEF) as EF = 1 − ESP/P_{max} and of Tau (logistic) = −(anti-epad – dia)/(2 × dpdt_min). Upper panel: Drawing of a right ventricular pressure curve with all detection points necessary for the calculation of RVEF and Tau. Lower panel: Drawing of the first derivative of right ventricular pressure over time. EF, ejection fraction; ePAD, estimated pulmonary artery diastolic pressure; esp, right ventricular endsystolic pressure; p_{Cross}, unadjusted isovolumetric contraction pressure; p_{max}, adjusted isovolumetric contraction pressure; sys, right ventricular systolic pressure.

as the right ventricular pressures and ePAD as described previously.[6] For the statistical analysis the day of insertion was set as Day 0. Values of variables were compared either at the start and end or over time of the measurement period between and within the two groups. The null hypothesis was, that there was no difference in values of variables at the beginning and end or over time of the measurement period between or within the two groups. Statistical evaluation was performed with the SPSS package 25.0, IBM. After checking for normal distribution (Shapiro–Wilk test and Kruskal–Wallis test) biometrical, clinical, and comorbidity data, RVEF and relaxation time constant Tau as well as pressure data, at Day 1 and as well as on the last day of the probe in place, were compared between the two groups by using a Student's *t* test or in case of not normal distribution by a Mann–Whitney *U* test. Thereafter comparison of values of RVEF and right ventricular diastolic isovolumetric relaxation time constant Tau and of all pressure values over time within each group was done by a linear mixed effect model to evaluate a possible effect of the vasodilators used. The null hypothesis was rejected and a significant difference between the two groups was assumed with a *p* value of less than 0.05. No adjustments for multiple testing were made. All data are reported as the median and interquartile range (25th–75th percentile; IQR) if not stated otherwise.

RESULTS

We evaluated 39 patients with a median recording time of 23 days (IQR: 5–30). Table 1 shows the biometrical and clinical data divided into survivors and nonsurvivors. There were no differences between both groups. Stepwise backward logistic regression of all variables with survival as the dependent variable showed significance for the RVSP for the first measurement day, the ePAD pressure for the first and the last measurement day, and

TABLE 1 Biometrical and clinical variables ($n = 39$)

Variable	Total ($n = 39$)	Survivors ($n = 25$)	Nonsurvivors ($n = 14$)	*p* Value
Age	57 (49–66)	52 (45–65)	61 (55–69)	0.028
Males [*n*], (%)	33 (85)	21 (84)	12 (86)	1.0
Hospital stay (days)	32 (21–53)	39 (24–55)	20 (11–38)	0.19
ICU stay (days)	27 (17–44)	31 (18–48)	19 (11–38)	0.92
Duration NIV (days)	1 (1–4)	1 (0–4)	2 (1–6)	0.288
Duration INV (days)	23 (12–38)	26 (15–40)	16 (9–33)	0.169
Patients with ECMO (*n*)	32	20	12	1.0
Duration ECMO (days)	12 (6–28)	12 (4–29)	12 (5.75–28)	0.988
paO_2/FiO_2 on the day of admission (mmHg)	86 (66–101)	86 (64–97)	85 (70–105)	0.861
paO_2/FiO_2 on the day of RV probe insertion (mmHg)	114 (93–162)	139 (93–176)	106 (90–135)	0.088
SAPS II	32 (26–36)	32 (26–35)	34 (27–44)	0.387
SOFA	6 (4–8)	6 (4–8)	6 (5–7)	0.723
PTE	7 (18)	6 (24)	1 (7)	0.386
CPR	8 (21)	3 (12)	5 (36)	0.109
Use of pulmonary vasodilators	32 (82)	19 (76)	13 (93)	0.386

Note: Data represent (%) or (IQR: 25–75) as indicated. *p* values represent results of the *T* test, χ^2 test, Mann–Whitney *U* test, or Kruskal–Wallis test.

Abbreviations: CPR, cardiopulmonary resuscitati; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; INV, invasive ventilation; NIV, noninvasive ventilation; paO_2, partial pressure of oxygen; PTE, pulmonary thromboendarterectomy; SAPS II, simplified acute physiology score II.

TABLE 2 Multivariate logistic regression with backward stepwise likelihood ratio ($n = 39$)

Variable	*p* Value	Odds ratio	95% CI
EPAD first day	0.024	0.609	0.396–0.937
SYS first day	0.044	1.319	1.008–1.726
EPAD last day	0.013	1.393	1.074–1.808
EF Shih last day	0.013	0.782	0.643–0.950

Note: Please refer to the text for a detailed prescription.

Abbreviations: CI, confidence interval; EF Shih, right ventricular ejection fraction calculated in %; EPAD, estimated pulmonary diastolic arterial pressure, all in mmHg; SYS, systolic right ventricular pressure.

the RVEF for the last measurement day as a discriminating variable between survivors and nonsurvivors (Table 2).

Figure 3a shows the course of the RVSP, right ventricular diastolic pressure and ePAD with RVEF and Tau for the 25 survivors over time, and Figure 3b shows the course of the same variables for the 14 nonsurvivors over time. The linear mixed effect model showed that there was a significant increase in RVEF due to the pulmonary vasodilators over time in the survivors (estimate: 0.354; 95% confidence interval, CI: 0.18–0.53; $p < 0.001$) but not in the nonsurvivors, where the observed RVEF decrease was not significant, probably because of the small number of patients. Tau increased significantly in the nonsurvivors (estimate: 0.001; 95% CI: 0.0004–0.0018; $p < 0.002$) but not in the survivors. Compared to the survivors, the amplitude of the right ventricular pressure in the nonsurvivors increased substantially, although not significantly, probably also because of the small number of patients.

Table 3 shows the data for the first and the last day of the probe in place for the right ventricular pressures along with the RVEF and Tau for survivors compared to nonsurvivors. There were substantial and significant differences on the last day of measurements between the RVSP, the ePAD, and most remarkably the RVEF, with the latter being 10% higher in the survivors compared to the nonsurvivors.

Table 4 shows the comparison of variables on the first and the last day of the probe in place within the survivors ($n = 25$) and the nonsurvivors ($n = 14$). Compared to the first measurement day in the survivors RVSP had decreased significantly on the last measurement day. In the nonsurvivors, ePAD had increased significantly on the last compared to the first measurement day.

DISCUSSION

There are three messages of this retrospective beat-to-beat calculation of RVEF and Tau from long-term continuous invasive measurements of right ventricular and ePAD pressures in 39 patients with severe COVID-19 ARDS:

1. The calculated RVEF's during the measurement period was very low in survivors (24%) and in nonsurvivors (23%; $p = 0.397$ survivors vs. nonsurvivors) indicating severe right ventricular dysfunction. In contrast, the isovolumetric relaxation time constant Tau of the right ventricle was in the normal range (0.027–0.033 s) both in survivors and in nonsurvivors.
2. Analysis of beat-to-beat RVEF and Tau over time from continuously measured right ventricular pressures unraveled early contrary trends in surviving COVID-19 ARDS patients showing an increase in RVEF with Tau remaining unchanged—potentially an effect of the administration of pulmonary vasodilators. In contrast, in the nonsurviving patients, RVEF remained unchanged but Tau increased significantly.
3. On the last measurement day, median RVEF was substantially and significantly higher and RVSP and ePAD significantly lower in the survivors compared to the nonsurvivors, possibly also indicating an effect of the administration of pulmonary vasodilators.

The present data are the first long-term evaluation of RVEF and Tau (up to 30 days) derived from continuous invasive registration of right ventricular pressures in COVID-19 patients with severe ARDS. Our findings are in line with several echocardiographic studies showing that up to 70% of mechanically ventilated COVID-19 patients had right ventricular dysfunction measured as decreased RVEF.[4,5,17,18] Since right ventricular dysfunction along with right ventricular and PH measured by echocardiography are prognostic factors for a poor outcome in COVID-19 patients continuous monitoring of RVEF along with RVSP and ePAD might improve decision-making and evaluation of treatments.[2,18–20] For example, in the present study, 19/25 survivors and 13/14 nonsurvivors, respectively, showed an increase in right ventricular pressures above 40 mmHg in the course of their COVID-19 ARDS. Since other treatments are not available, we applied the pulmonary vasodilators sildenafil alone or in combination with inhaled iloprost or nitric oxide. Consecutively in the survivors, RVEF increased and RVSP decreased

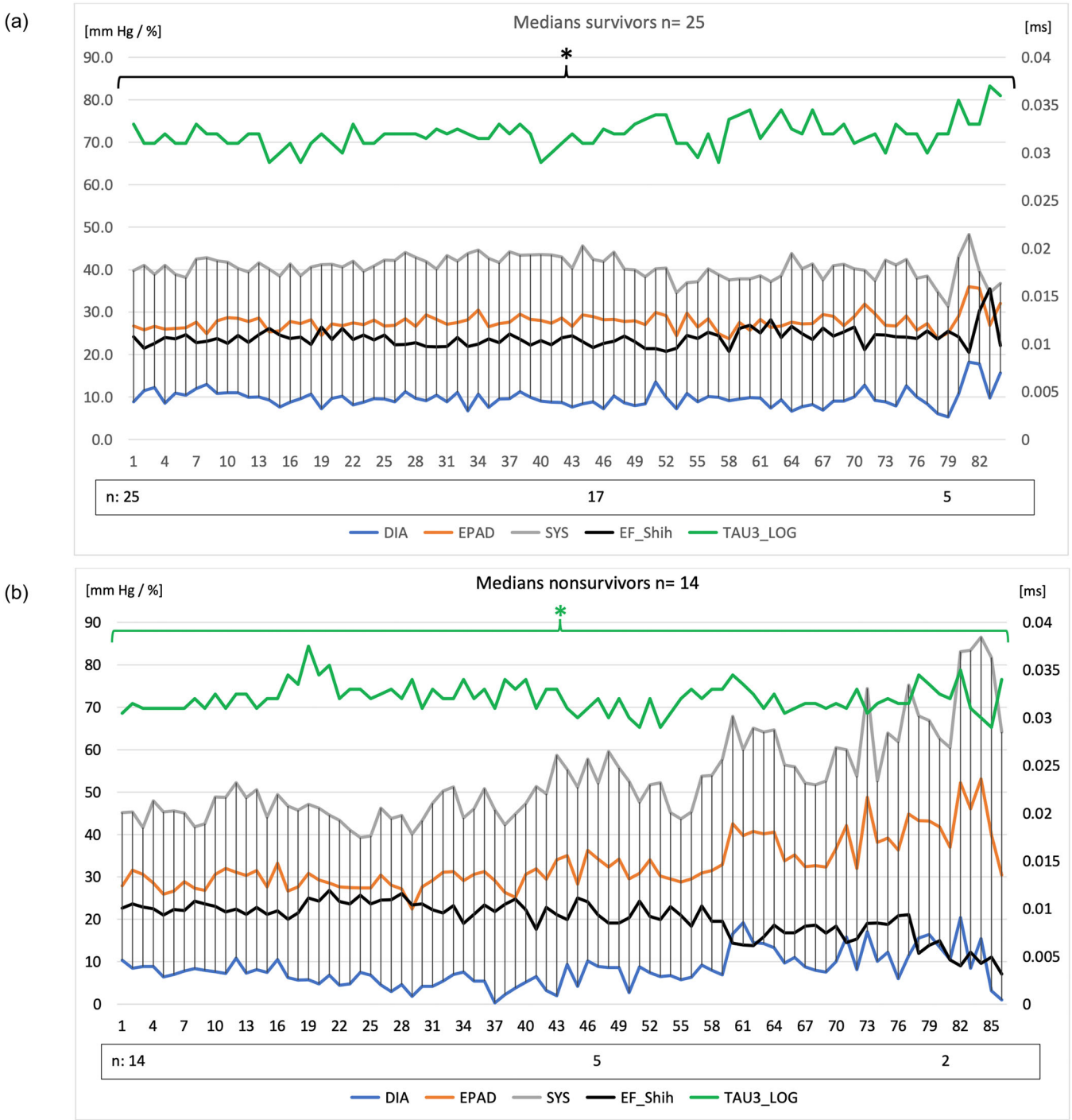


FIGURE 3 A time course of right ventricular and estimated pulmonary artery diastolic pressures along with right ventricular ejection fraction (RVEF) and Tau over time of the surviving (a, $n = 25$) and the nonsurviving patients (b, $n = 25$; *$p < 0.05$ for increased in RVEF over time). (b) Time course of right ventricular and estimated pulmonary artery diastolic pressures along with right ventricular ejection fraction and Tau over time of the nonsurviving patients (b, $n = 14$). (*$p < 0.05$ for an increase in TAU over time). DIA, right ventricular diastolic pressure; EF-Shih, right ventricular ejection fraction; EPAD, estimated pulmonary artery diastolic pressure; SYS, right ventricular systolic pressure; TAU3_log, time constant of isovolumetric relaxation time.

significantly in the survivors over time but remained unchanged in nonsurvivors.

Since the importance of PH in COVID-19 ARDS is not clear, we are aware that our treatment with pulmonary vasodilators in patients with COVID-19 ARDS was not evidence-based since until today no prospective study has convincingly shown a survival benefit in those patients treated with inhaled and/or systemic pulmonary vasodilators.

TABLE 3 Comparison of variables on the first and the last day of the right ventricular catheter in place between survivors ($n = 25$) versus nonsurvivors ($n = 14$)

Variable	Median (IQR) survivors	Median (IQR) nonsurvivors	*p* Value
DIA first day	9 (5–13)	10 (2–12)	0.602
DIA last day	7 (2–11)	9 (3–16)	0.102
SYS first day	40 (34–45)	45 (36–50)	0.422
SYS last day	37 (30–40)	48 (41–52)	0.001
EPAD first day	27 (21–31)	28 (23–30)	0.907
EPAD last day	26 (23–29)	30 (27–34)	0.008
EF Shih first day	24 (20–29)	23 (17–27)	0.397
EF Shih last day	25 (22–29)	15 (11–23)	0.001
TAU3_log first day	0,029 (0.027–0.033)	0.029 (0.028–0.031)	0.965
TAU3_log last day	0,029 (0.027–0.032)	0.029 (0.028–0.032)	0.828

Note: Data represent the results of a *T* test in case of a normal distribution or a Mann–Whitney *U* test in case of not normal distribution (TAU3_log) of the variables. Please refer to the text for a detailed description.

Abbreviations: DIA, diastolic right ventricular pressure; EF Shih, right ventricular ejection fraction calculated in %; EPAD, estimated pulmonary diastolic arterial pressure, all in mm Hg; IQR, interquartile range; SYS, systolic right ventricular pressure; TAU3_log, time constant of right ventricular diastolic isovolumetric relaxation time calculated in milliseconds.

TABLE 4 Comparison of variables on the first and the last day of the right ventricular catheter in place within the survivors ($n = 25$) and the nonsurvivors ($n = 14$)

Variable (median [IQR])	Survivors first day	Survivors last day	*p* Value
DIA	9 (5–13)	7 (2–11)	0.062
SYS	40 (34–45)	37 (30– 40)	0.043
EPAD	27 (21–31)	26 (23–29)	0.261
EF Shih	24 (20–29)	25 (22–29)	0.820
TAU3_log	0,029 (0.027–0.033)	0,029 (0.027–0.032)	0.560
	Nonsurvivors first day	***Nonsurvivors last day***	
DIA	10 (2–12)	9 (3–16)	0.146
SYS	45 (36–50)	48 (41–52)	0.316
EPAD	28 (23–30)	30 (27–34)	0.011
EF Shih	23 (17–27)	15 (11–23)	0.760
TAU3_log	0.029 (0.028–0.031)	0.029 (0.028–0.032)	0.081

Note: Data represent the results of a *T* test in case of a normal distribution or a Mann–Whitney *U* test in case of not normal distribution (TAU3_log) of the variables. Please refer to the text for a detailed prescription.

Abbreviations: DIA, diastolic right ventricular pressure; EF Shih, right ventricular ejection fraction calculated in %; EPAD, estimated pulmonary diastolic arterial pressure, all in mmHg; IQR, interquartile range; SYS, systolic right ventricular pressure; TAU3_log, right ventricular diastolic isovolumetric relaxation time constant calculated in seconds.

Moreover, recalculation of mean PAP from our data in the surviving and the nonsurviving patients revealed, that, compared to the current definition of PH, the resulting mean PAP (survivors vs. nonsurvivors first vs. last measurement: 31 vs. 30 and 34 vs. 36 mmHg) was rather in the mild to moderate range of PH (20–35 mmHg) and would not be expected to impair RV function. In addition, the application of PEEP as standard

treatment in ARDS patients could also have played a role. Thus, our data of decreased RVEF and increased Tau show that in COVID-19 ARDS the RV may fail in spite of normal or mildly elevated PAP.[21]

RVEF's as low as 25% have been found by gated blood pool scintigraphy in patients suffering from PH. However, no consistent relationship between PH defined as mean PAP of ≥20 mm hg and an RVEF ≤ 45% could be shown in that study.[22] In contrast, Heerdt et al.[7,8] showed recently, that pressure-based single beat estimation of RVEF in patients with PH correlated with RVEF measured by MRI. Moreover, in their comparison, they found RVEF as low as 15% with both the single beat method and MRI in the same patients.[8] Thus, the low RVEF found in our patients with COVID-19 ARDS might reflect severe right ventricular dysfunction probably evoked by ARDS-induced acute PH.

Tau is accepted as a marker of diastolic function and has been shown to be correlated to the isovolumetric relaxation time of the left ventricle in animals, healthy humans, and patients with PH.[10,23–25] However, while until today, little attention has been paid to the evaluation of Tau neither in healthy nor in diseased patients the increasing prevalence and incidence of patients with heart failure with preserved ejection fraction has renewed the interest in an easily and reproducibly calculable variable for the assessment of diastolic function in humans.[10] Our data are the first long-term assessment of right ventricular diastolic function by the calculation of the time constant Tau of the right ventricle in patients with acute right ventricular hypertension induced by COVID-19 ARDS. Although in our patients, Tau increased significantly over time in the nonsurvivors and remained unchanged in the surviving patients, all calculated values of Tau were in the range that is currently believed to be physiological.[9,24] While in patients with chronic PH Tau is substantially and significantly higher (+60%) compared to healthy subjects no data of changes in Tau from patients with acute right ventricular and PH are available.[9] Accordingly, the physiological values of Tau obtained in our patients may merely reflect the difference between acute versus chronic increases in right ventricular and pulmonary artery pressures.

The continuous long-term registration of right ventricular systolic pressure by an ultrathin probe in patients with PH is for several reasons of special interest: first, transthoracic echocardiography substantially underestimated in 60% of patients with PH the true RVSP and PAP measured by right heart catheterization, and second, a pulmonary artery catheter because of its wide range of complications can be left in place only for few days.[25,26] Thus, continuous long-term monitoring of RVSP and ePAD is the only way to reliable detection and treatment of right ventricular hypertension, PH, and consecutive changes in RVEF.[27,28] Our findings of excessive acute right ventricular and thus PH over days and weeks are clearly clinically relevant in view of the relationship of a substantially increased mortality in patients with PH suffering from COVID-19-induced ARDS.[1,20,29]

We confirmed our previous finding of a significantly higher ePAD in the nonsurvivors compared to the surviving patients at the end of the measurement period.[6] While an ePAD above 23 mmHg has been shown to be a sensitive indicator not only for acute cardiac decompensation but also for long-term mortality in patients with heart failure the increase or decrease of ePAD—like the increases or decreases of right ventricular pressures or RVEF - in our patients might also depend on factors like development of acute PH by ARDS, changes in volume status or use of vasodilators or vasopressors with sometimes considerable fluctuations over time.[30]

Critique of methods

The strength of our retrospective analysis is the duration of continuous measurement of right ventricular pressures and thus to derive RVEF and Tau in patients with COVID-19 ARDS showing the development of right ventricular hypertension with concomitant decreases in RVEF and increases Tau in the course of the disease. Whatever intervention—pulmonary vasodilators, infection control, renal replacement therapy, and/or venovenous ECMO—might have been the reason for the decrease in RVSP and the increase in RVEF over time in the surviving patients, continuous measurement of right ventricular and estimated pulmonary artery pressures enabled us to monitor the right ventricle as a prognostic relevant target in patients with a high risk of mortality.[2,31,32]

For RVEF we modified the algorithm originally published by Shih et al.,[15] because this modification yields reliable detection of the points on the right ventricular pressure curve necessary for the calculation of both RVEF and Tau (see Figures 1 and 2 in Section 2).

The novel single-beat pressure approach for the calculation of RVEF has been validated by cardiac MRI in two studies with 31 patients suffering from PH or

heart failure with preserved ejection fraction.[7,8] For the calculation of Tau, we used the logistic approach as evaluated and proposed by Ogilvie et al.[10] We tested the reliability of our algorithms by manual evaluation of both RVEF and Tau, showing excellent correlation with automated calculation by our written software.

Study limitations

The main weakness of our analysis of RVEF and Tau is the retrospective offline design without controls. Therefore, the present analysis should be taken as hypothesis generating with the necessity of confirmation of our RVEF algorithm for example by three-dimensional echocardiography or cardiac magnetic resonance imaging in randomized controlled trials not only in patients with COVID-19 ARDS.[7,8,12,33]

Clinical application

Our next steps in the future are to translate our single-beat right ventricular pressure offline calculation of RVEF and Tau into continuous online monitoring of RVEF and Tau, thus introducing a continuous estimation of right ventricular systolic and diastolic function.[7,8,34] Ultimately, online remote control of changes in hemodynamics with continuous long-term monitoring of RVSP and RVEF as a diagnostic and therapeutic target in patients with acute and chronic heart failure seems to be possible and obviously has the potential to reduce hospitalization rates as well as mortality.[29,35]

AUTHOR CONTRIBUTIONS

Matthias Gaertner was responsible for the collection and preparation of the data and has run the statistical evaluation. Felix Glocker has developed the algorithm for the detection of the various pressure points on the right ventricular pressure curve and has written the evaluation software. Raymond Glocker and Hans-Bernd Hopf checked and approved all recorded pressure traces. Matthias Gaertner, Felix Glocker, and Hans-Bernd Hopf have written the manuscript. Raymond Glocker edited and reviewed the manuscript.

ACKNOWLEDGMENTS

The authors acknowledge the invaluable help of Dr. Natalie Filmann, staff statistician at the Institut für Biostatistik und Mathematische Modellierung, Zentrum der Gesundheitswissenschaften, Klinikum und Fachbereich Medizin der Goethe-Universität, Frankfurt am Main, Germany, in performing the adequate statistical analyses. Funding was done solely by the use of departmental resources. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

Felix Glocker, Raymond Glocker, and Hans-Bernd Hopf are shareholders of emka medical GmbH. Matthias Gaertner declares no conflict of interest.

ETHICS STATEMENT

This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Landesaerztekammer Hessen (File No. 2021-2415-evBO). Informed consent of all patients or their next relative was obtained.

ORCID

Matthias Gaertner http://orcid.org/0000-0001-5600-8325
Felix Glocker http://orcid.org/0000-0002-7805-8961

REFERENCES

1. Caravita S, Baratto C, Di Marco F, Calabrese A, Balestrieri G, Russo F, Faini A, Soranna D, Perego GB, Badano LP, Grazioli L, Lorini FL, Parati G, Senni M. Haemodynamic characteristics of COVID-19 patients with acute respiratory distress syndrome requiring mechanical ventilation. an invasive assessment using right heart catheterization. Eur J Heart Fail. 2020 Dec 7;22(12):2228–37.
2. Rath D, Petersen-Uribe Á, Avdiu A, Witzel K, Jaeger P, Zdanyte M, Heinzmann D, Tavlaki E, Müller K, Gawaz MP. Impaired cardiac function is associated with mortality in patients with acute COVID-19 infection. Clin Res Cardiol. 2020 Dec 20;109(12):1491–9.
3. Smith N, Tampakakis E. COVID-19 acute respiratory distress syndrome: intriguing haemodynamics of an intriguing syndrome. Eur J Heart Fail. 2021 Feb;23(2):208–10.
4. Corica B, Marra AM, Basili S, Cangemi R, Cittadini A, Proietti M, Romiti GF. Prevalence of right ventricular dysfunction and impact on all-cause death in hospitalized patients with COVID-19: a systematic review and meta-analysis. Sci Rep. 2021 Dec;11(1):17774.
5. Isgro G, Yusuff HO, Zochios V. The right ventricle in COVID-19 lung injury: proposed mechanisms, management, and research gaps. J Cardiothorac Vasc Anesth. 2021 Jun 2;35(6):1568–72.
6. Gaertner M, Glocker R, Glocker F, Hopf HB. Continuous long-term wireless measurement of right ventricular pressures and estimated diastolic pulmonary artery pressure in patients with severe COVID-19 acute respiratory distress syndrome. ESC Heart Fail. 2021 Dec;8(6):5213–21.
7. Heerdt PM, Kheyfets V, Charania S, Elassal A, Singh I. A pressure-based single beat method for estimation of right ventricular ejection fraction: proof of concept. Eur Respir J. 2020 Mar;55(3):1901635.

8. Heerdt PM, Singh I, Elassal A, Kheyfets V, Richter MJ, Tello K. Pressure-based estimation of right ventricular ejection fraction. ESC Heart Fail. 2022 Apr;9(2):1436–43.
9. Murch SD, La Gerche A, Roberts TJ, Prior DL, MacIsaac AI, Burns AT. Abnormal right ventricular relaxation in pulmonary hypertension. Pulm Circ. 2015 Jun;5(2):370–5.
10. Ogilvie LM, Edgett BA, Huber JS, Platt MJ, Eberl HJ, Lutchmedial S, Brunt KR, Simpson JA. Hemodynamic assessment of diastolic function for experimental models. Am J Physiol-Heart Circ Physiol. 2020 May 1;318(5): H1139–58.
11. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med. 2018 May 24;378(21):1965–75.
12. Vanderpool RR, Puri R, Osorio A, Wickstrom K, Desai AA, Black SM, Garcia JGN, Yuan JXJ, Rischard FP. Surfing the right ventricular pressure waveform: methods to assess global, systolic and diastolic RV function from a clinical right heart catheterization. Pulm Circ. 2020 Jan;10(1):1–11.
13. Bellofiore A, Vanderpool R, Brewis MJ, Peacock AJ, Chesler NC. A novel single-beat approach to assess right ventricular systolic function. J Appl Physiol. 2018 Feb 1;124(2):283–90.
14. Sunagawa K, Yamada A, Senda Y, Kikuchi Y, Nakamura M, Shibahara T, Nose Y. Estimation of the hydromotive source pressure from ejecting beats of the left ventricle. IEEE Trans Biomed Eng. 1980 Jun;27(6):299–305.
15. Shih H, Hillel Z, Declerck C, Anagnostopoulos C, Kuroda M, Thys D. An algorithm for real-time, continuous evaluation of left ventricular mechanics by single-beat estimation of arterial and ventricular elastance. J Clin Monit. 1997;13(3):157–70.
16. Brimioulle S, Wauthy P, Ewalenko P, Rondelet B, Vermeulen F, Kerbaul F, Naeije R. Single-beat estimation of right ventricular end-systolic pressure-volume relationship. Am J Physiol-Heart Circ Physiol. 2003 May 1;284(5): H1625–30.
17. Gibson LE, Fenza RD, Lang M, Capriles MI, Li MD, Kalpathy-Cramer J, Little BP, Arora P, Mueller AL, Ichinose F, Bittner EA, Berra L, G. Chang M. Right ventricular strain is common in intubated COVID-19 patients and does not reflect severity of respiratory illness. J Intensiv Care Med. 2021 Aug;36(8):900–9.
18. Bleakley C, Singh S, Garfield B, Morosin M, Surkova E, Mandalia MS, Dias B, Androulakis E, Price LC, McCabe C, Wort SJ, West C, Li W, Khattar R, Senior R, Patel BV, Price S. Right ventricular dysfunction in critically ill COVID-19 ARDS. Int J Cardiol. 2021 Mar;327:251–8.
19. Wats K, Rodriguez D, Prins KW, Sadiq A, Fogel J, Goldberger M, Moskovits M, Tootkaboni MP, Shani J, Jacob J. Association of right ventricular dysfunction and pulmonary hypertension with adverse 30-day outcomes in COVID-19 patients. Pulm Circ. 2021 Apr;11(2):1–9.
20. Holmqvist J, Beck-Friis J, Jensen C, Dalla K, Mårdstam S, Christensen J, Nordén N, Widing H, Rosén-Wetterholm E, Cavefors O, Yilmaz A, Cronhjort M, Redfors B, Oras J. Cardiac dysfunction and mortality in critically ill patients with COVID-19: a Swedish multicentre observational study. Acta Anaesthesiol Scand. 2022 May;66(5):606–14.
21. Hoeper MM, Barberà JA, Channick RN, Hassoun PM, Lang IM, Manes A, Martinez FJ, Naeije R, Olschewski H, Pepke-Zaba J, Redfield MM, Robbins IM, Souza R, Torbicki A, McGoon M. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol. 2009 Nov;54(1 Suppl):S85–96.
22. Morrison D, Goldman S, Wright AL, Henry R, Sorenson S, Caldwell J, Ritchie J. The effect of pulmonary hypertension on systolic function of the right ventricle. Chest. 1983 Sep;84(3): 250–7.
23. Thomas JD, Flachskampf FA, Chen C, Guererro JL, Picard MH, Levine RA, Weyman AE. Isovolumic relaxation time varies predictably with its time constant and aortic and left atrial pressures: implications for the noninvasive evaluation of ventricular relaxation. Am Heart J. 1992 Nov;124(5): 1305–13.
24. Varma SK, Owen RM, Smucker ML, Feldman MD. Is tau a preload-independent measure of isovolumetric relaxation? Circulation. 1989 Dec;80(6):1757–65.
25. Nathan SD, Shlobin OA, Barnett SD, Saggar R, Belperio JA, Ross DJ, Ahmad S, Saggar R, Libre E, Lynch JP, Zisman DA. Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med. 2008 Sep; 102(9):1305–10.
26. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA. 2005 Oct 5;294(13):1625–33.
27. Zochios V, Parhar K, Tunnicliffe W, Roscoe A, Gao F. The right ventricle in ARDS. Chest. 2017 Jul;152(1):181–93.
28. Park JF, Banerjee S, Umar S. In the eye of the storm: the right ventricle in COVID-19. Pulm Circ. 2020 Sep;10(3):1–7.
29. Norderfeldt J, Liliequist A, Frostell C, Adding C, Agvald P, Eriksson M, Lönnqvist PA. Acute pulmonary hypertension and short-term outcomes in severe Covid-19 patients needing intensive care. Acta Anaesthesiol Scand. 2021 Jul;65(6): 761–9.
30. Zile MR, Bennett TD, El Hajj S, Kueffer FJ, Baicu CF, Abraham WT, Bourge RC, Warner Stevenson L. Intracardiac pressures measured using an implantable hemodynamic monitor: relationship to mortality in patients with chronic heart failure. Circ Heart Fail. 2017 Jan; 10(1):e003594.
31. Miranda DR, van Thiel R, Brodie D, Bakker J. Right ventricular unloading after initiation of venovenous extracorporeal membrane oxygenation. Am J Respir Crit Care Med. 2015 Feb 1;191(3):346–8.
32. Pishgahi M, Karimi Toudeshki K, Safari S, Yousefifard M. Echocardiographic abnormalities as independent prognostic factors of in-hospital mortality among COVID-19 patients. Arch Acad Emerg Med. 2021;9(1):21.
33. Greiner S, André F, Heimisch M, Aurich M, Steen H, Katus HA, Mereles D. A closer look at right ventricular 3D

volume quantification by transthoracic echocardiography and cardiac MRI. Clin Radiol. 2019 Jun;74(6):490.
34. Naeije R, Richter MJ, Vanderpool R, Tello K. When it all comes down to pressure: right ventricular ejection fraction at cardiac catheterisation. Eur Respir J. 2020 Mar;55(3): 1902341.
35. Jain CC, Borlaug BA. Hemodynamic assessment in heart failure. Catheter Cardiovasc Interv. 2020 Feb 15;95(3): 420–8.

How to cite this article: Gaertner M, Glocker R, Glocker F, Hopf H-B. Pressure-based beat-to-beat right ventricular ejection fraction and Tau from continuous measured ventricular pressures in COVID-19 ARDS patients. Pulm Circ. 2023;13:e12179. https://doi.org/10.1002/pul2.12179