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

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Abstract

Aims We continuously monitored right ventricular pressures and the estimated diastolic pulmonary artery pressure (ePAD) for up to 30 days in mechanically ventilated patients with severe COVID-19 acute respiratory distress syndrome in order to detect and treat right ventricular and pulmonary artery hypertension.

Methods and Results We retrospectively evaluated right ventricular pressures and the ePAD measured in 30 invasively ventilated COVID-19 acute respiratory distress syndrome patients between 1 October 2020 and 31 March 2021. We divided the patients into two groups, survivors and non-survivors based on their 60 day mortality. Primary outcome variables were the values of right ventricular pressures and the ePAD over time after insertion of the right ventricular probe. Right ventricular systolic pressure \(RVSP\) \((IQR; 25th \text{ to } 75th \text{ percentile})\) was significantly lower on the first and the last measurement day in the survivors compared with the non-survivors \(\text{Day 1: } 38 (27–45) \text{ vs. } 46 (44–49), P = 0.036; \text{ last day: } 36 (27–44) \text{ vs. } 51 (40–57) \text{ mmHg, } P = 0.006\). 16/22 survivors and 7/8 non-survivors received sildenafil orally, one survivor received additionally inhaled nitric oxide and one survivor and one non-survivor each inhaled iloprost. On the last measurement day, both right ventricular pressure amplitude \(31 (26–37) \text{ vs. } 38 (35–47) \text{ mmHg, } P = 0.027\) and ePAD \(22 (16–26) \text{ vs. } 31 (23–34) \text{ mmHg, } P = 0.043\) were significantly lower in the survivors compared with the non-survivors. Four patients in the survivor group developed excessive high RVSP in the course of their disease (peak: 57/61/78/105 mmHg). After sildenafil 20 mg every 8 h, additional inhaled nitric oxide (20 ppm) in one and additional inhaled iloprost 20 \(\mu g\) every 4 h in another patient RVSP consecutively decreased substantially in all four patients until the end of the measurement period (47/23/42/47 mmHg).

Conclusions The RVSP and right ventricular pressure amplitude both were significantly lower in the survivors compared with those in the non-survivors with a significant decrease in RVSP over time in the survivors suggesting successful lowering by pulmonary vasodilators. The ePAD as an indicator of left heart failure was significantly higher in non-survivors compared to the surviving patients.

Keywords COVID-19; ARDS; Pulmonary hypertension; ePAD; Sildenafil

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Introduction

The pathophysiology of acute respiratory distress syndrome (ARDS) associated with COVID-19 pneumonia is not yet understood. Recent data suggest that development of pulmonary artery hypertension (PAH) in combination with right ventricular hypertension might be one of the key features associated with a worse prognosis.1–3 However, monitoring of right ventricular and pulmonary arterial haemodynamic is not easily feasible. Echocardiography is
non-invasive but lacks continuous measurement and is depending on the performing physician. Using a pulmonary artery catheter is invasive, not without infectious risks, the catheter cannot be used when patients are mobilized and, most importantly, continuous monitoring over more than a few days is not feasible. However, right ventricular systolic pressure equals pulmonary artery systolic pressure in the absence of an outflow obstruction of the right ventricle. Accordingly, we used in mechanically ventilated patients with severe ARDS caused by COVID-19 pneumonia a newly developed 3 French catheter tip probe for long-term application in the right ventricle for wireless continuous measurements of right ventricular pressures and the estimated diastolic pulmonary artery pressure (ePAD) to detect and treat right ventricular hypertension and PAH. Here we present the preliminary results.

Methods

Patient selection

With approval of the local ethical committee (LAEK Hessen 2021-2415-evBO) we retrospectively evaluated 30 invasively ventilated patients with severe COVID-19 ARDS confirmed by a positive PCR test and a native or contrast media enforced thoracic computed tomography scan showing COVID-19 typical opacified pulmonary infiltrations in whom a right ventricular pressure probe for continuous long-term (i.e. up to 30 days) right ventricular pressure measurement has been inserted between 1 October 2020 and 31 March 2021. In all patients, informed consent of the patient or its next relative was obtained before insertion of the catheter. In 22/30 patients, veno-venous extracorporeal membrane oxygenation (ECMO) has been instituted along the guidelines as described previously by Combes et al. Standard ECMO settings were 3000–3500 rpm to generate a flow between 3.5 and 4.5 lpm to achieve a \( \text{paO}_2 \geq 60 \text{ mmHg} \) and a sweep-flow to achieve a \( \text{paCO}_2 \leq 60 \text{ mmHg} \) with a pH value \( \geq 7.30 \). All patients breathed spontaneously in the pressure assist mode. With exception of a continuous infusion of sufentanil, no sedatives were used. If clinically indicated, clonidine or dexmedetomidine were added to achieve a Richmond Agitation Sedation Score of 0-1.

CorLog probe implantation and functions

In all patients CorLog Probe 1P, (EMKA Medical GmbH, Aschaffenburg, Germany) was used for continuous right ventricular pressure measurement. CorLog Probe 1P is a high fidelity pressure measurement system designed for long-term use in the right atrium or the right ventricle (40 or 35 cm long, Figure 1) using Fluorinert® fluid instead of sodium chloride as transmission fluid. The diameter of the probe is 1.1 mm (3 F).

The use in our patients was permitted by the 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 4 April 2017. For each patient, a separate indication sheet had to be filled out by H. B. H. before insertion of the probe. The CorLog System analysis and evaluation by CorLog App got CE-0482 mark on 7 April 2021.

The right ventricular pressure probe was inserted percutaneously under aseptic conditions via the left or right subclavian vein with a 6 F split introducer cannula under local infiltration analgesia. Placement of the probe was guided by continuous pressure measurement while advancing the probe until typical right ventricular pressure curves could be recorded. After 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 (Figure 2). After the insertion of the probe, the system needed 24 h for temperature equilibration.

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/cm³), 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 a 30 days in-vitro stability of 0.5 mmHg.

Pressure recordings were transmitted to the intensive care unit (ICU) bedside monitor via an interface (Connect) for continuous right ventricular pressure monitoring and to a standard smartphone equipped with the CorLog application software (App). CorLog Connect streamed in analogue format along IEC 60601-2-34 the right ventricular pressure data in an uninterrupted continuous analogue signal voltage ‘stream’ to the invasive blood pressure module of the patient monitor.
All other data from CorLog Probe 1P (probe temperature, data of the three dimensional accelerometer located within the housing of CorLog Probe 1P to detect movements of the patient and the 1st derivative of dp/dt max of the right ventricular pressure tracing) were stored in the smartphone by CorLog App for later analysis.

The location of the probe was checked and confirmed several times per day and within the routine intensive care unit rounds by H. B. H. Right ventricular pressure and right ventricular dp/dt max were continuously recorded throughout the time the probe was in place. Maximal duration of pressure recordings for one probe system was 30 days.

After removal of the system, all data were extracted to a data evaluation tool for offline analysis. Right ventricular systolic (RVSP) and diastolic pressure (RVDP) as well as the pressure amplitude (RVPAMPL) were obtained from the recordings. ePAD was calculated as described previously.8,9

A typical recording is shown in Figure 3. In the left upper corner of the figure, the explanations of each graph and line are depicted. The opening of the pulmonary artery valve is indicated by high frequent parts of the measurements, which is exactly congruent to the maximum of dp/dt (dashed vertical red line) as indirect indicator of the opening of the pulmonary artery valve for calculation of ePAD from the right ventricular pressure (dashed vertical green line). The dashed blue line represents the diastolic right ventricular pressure necessary for the calculation of the right ventricular pressure amplitude.

After extracting the data from each smartphone all original right ventricular tracings were checked visually by H. B. H., F. G., and R. G. 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 a.m. to 8 a.m., 3 p.m. to 4 p.m., and 11 p.m. to 12 a.m. 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 co-morbidity data as well as SAPS 2 and SOFA-score at the start of mechanical

Figure 2 CorLog Probe 1P after implantation in one patient via the right subclavian vein. The housing is fixed within the fossa infraclavicularis by four sutures.

Figure 3 A typical example of a right ventricular pressure recording along with the respective dp/dt tracing. ePAD, estimated diastolic pulmonary artery pressure; RVSP, right ventricular systolic pressure.
ventilation therapy were recorded. Also, for each patient, start and end as well as dosage of pulmonary artery vasodilators (oral sildenafil and/or inhaled iloprost and/or inhaled NO) were recorded. Duration of non-invasive and invasive ventilation as well as duration of the extracorporeal membrane oxygenation were also recorded from the patients records and stored in the excel spreadsheet. The presence of pulmonary artery embolism as revealed by single or repetitive contrast media enforced thoracic computed tomography scans were also recorded in the spreadsheet. Horowitz index was determined at 5 day intervals to evaluate progress of pneumonia.

Statistical methods

After evaluation of the data of all patients, we used 60 day mortality to separate the patients into two groups: survivors (Group 1, n = 22) and non-survivors (Group 2, n = 8). Primary outcome variables were the values of RVSP, RVDP, RVPAMPL, and ePAD measured over time after insertion of the right ventricular probe. For the statistical analysis, the day of insertion was set as Day 0. Values of variables were compared either at start and end or over time of measurement period between and within the two groups. Null hypothesis was that there was no difference in values of variables at start 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, USA. After checking for normal distribution (Shapiro-Wilk test) biometrical, clinical and co-morbidity data, 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. A logistic regression of all variables of the whole group of 30 patients with survival as dependent variable was performed. The regression was carried out stepwise backwards. Thereafter, comparison of pressure data over time within each group was carried out by a linear mixed-effect model to evaluate a possible effect of the vasodilators used. 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 median and range if not stated otherwise.

Results

We evaluated 30 patients with a median recording time of 22 days (Range 7–30). Logistic regression of all variables evaluated showed significance only for the RVSP of the last measurement as discriminating variable between survivors and non-survivors (P = 0.033; odds ratio = 1.126; 95% confidence interval = 1.010–1.257). Table 1 shows the biometrical and clinical data divided in survivors and non-survivors. There were no differences between both groups.

Figure 4A shows the course of the RVSP, RVDP, and ePAD of the 22 survivors over time; Figure 4B shows the course of the RVSP, RVDP, and ePAD of the 8 non-survivors over time. The linear mixed-effect model showed that there was a significant decrease in RVSP due to the pulmonary vasodilators over time in the survivors (estimate: −0.38; 95% confidence interval = −0.59 to −0.17; P < 0.001) but not in the non-survivors. Compared with the survivors, the amplitude of the right ventricular pressure in the non-survivors increased slowly, but not significantly.

Table 1 Biometrical, clinical and co-morbidity data of the patients

| Variable                        | Total (n = 30) | Survivors (n = 22) | Non-survivors (n = 8) | P value |
|---------------------------------|---------------|-------------------|----------------------|--------|
| Age (year)                      | 53.5 [43.5 – 64.75] | 49.0 [39.0 – 64.5] | 57.0 [52.0 – 70.0] | 0.101 |
| Sex (male)                      | 26 (86.7)     | 19 (86.4)         | 7 (87.5)             | 0.939 |
| Duration ICU stay (days)        | 25.5 [17.25 – 49.5] | 31.0 [20.0 – 52.0] | 18.0 [11.0 – 24.0] | 0.162 |
| Duration NIV (days)             | 1.0 [0.25 – 3.75] | 1.0 [0.25 – 3.5]  | 1.0 [1.0 – 7.0]     | 0.950 |
| Duration invasive ventilation (days) | 21.5 [14.25 – 40.25] | 26.0 [18.0 – 45.0] | 15.0 [9.0 – 19.0] | 0.187 |
| ECMO (%)                        | 24 (80.0)     | 17 (77.3)         | 7 (87.5)             | 0.552 |
| Duration ECMO (days)            | 13.0 [8.25 – 29.5] | 14.0 [9.0 – 34.0] | 9.0 [6.0 – 18.0]    | 0.510 |
| CPR (%)                         | 5 (16.7)      | 2 (9.1)           | 3 (37.5)             | 0.177 |
| PTE (%)                         | 5 (16.7)      | 4 (18.2)          | 1 (12.5)             | 0.723 |
| Vasodilator use (%)             | 23 (76.7)     | 16 (72.7)         | 7 (87.5)             | 0.415 |
| SOFA                            | 5.0 [4.0 – 6.0] | 4.5 [4.0 – 6.0]   | 5.5 [4.25 – 6.75]    | 0.209 |
| SAPS II                         | 32.0 [26.75 – 35.0] | 31.0 [25.0 – 35.25] | 33.0 [29.25 – 41.0] | 0.654 |
| Asthma/COPD (%)                 | 6 (20)        | 5 (22.7)          | 1 (12.5)             | 0.552 |
| BMI > 25 (%)                    | 10 (33.3)     | 8 (36.4)          | 2 (25.0)             | 0.576 |
| Diabetes mellitus II (%)        | 9 (30)        | 8 (36.4)          | 1 (12.5)             | 0.162 |
| Hypertension (%)                | 15 (50)       | 11 (50)           | 4 (50)               | 1.0   |
| Coronary heart disease (%)      | 2 (6.7)       | 2 (9.1)           | 0                   | 0.395 |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PTE: pulmonary artery embolism; SAPS II: simplified acute physiological score II; SOFA: sequential organ failure assessment score.

Data represent n (%) or median [IQR; 25th to 75th percentile].

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Figure 5A–D shows the data for the first and the last days of the probe in place for RVSP (A), RVDP (B), RVPAMPL (C), and ePAD (D) for survivors compared with non-survivors.

The RVSP (Figure 5A) at the first day after placement of the right ventricular probe was 38 mmHg [interquartile range (IQR) 27–45] in the survivors compared with 46 mmHg (IQR 44–48) in the non-survivors (P = 0.036 survivors vs. non-survivors). At the end of the measurement period, RVSP was 36 mmHg (IQR 27–44 mmHg) in the survivors compared with 51 mmHg (IQR 40–57) in the non-survivors (P = 0.006 survivors vs. non-survivors). In fact, in the survivors, RVSP had decreased in 13/22 patients, increased in 8/22, and remained unchanged in 1. In 16/22 patients, sildenafil (20 mg 3× per day) has been given orally, one of the patients received additionally inhaled nitric oxide (20 ppm) and one additional inhaled iloprost, 20 μg every 4 h had been added. In the non-survivors, RVSP increased in four and decreased slightly in the other four patients. Sildenafil was used in seven, additional inhaled iloprost in one patient.

There were four patients in the survivor group with excessive high RVSP in the course of their disease (peak: 57/61/78/105 mmHg). All received sildenafil 20 mg every 8 h, in one patient inhaled nitric oxide (20 ppm) and in another patient inhaled iloprost, 20 μg every 4 h had been added. RVSP consecutively decreased substantially in all four patients until the end of the measurement period (47/34/23/12 mmHg).

The RVDP on the first and the last days of the probe in place was not different between survivors compared to non-survivors (Figure 5B).

While RVPAMPL on measurement Day 1 was not different between survivors compared with non-survivors, there was a significant difference on the last day (Figure 5C). In fact, RVPAMPL was 31 mmHg (IQR 26–37) in the survivors compared with 38 mmHg (IQR 35–47) in the non-survivors (P = 0.027 survivors vs. non-survivors) resulting in a 7 mmHg lower amplitude in the survivors compared with the non-survivors.

The ePAD was significantly lower both on measurement Day 1 and on the last measurement day in the survivors compared with the non-survivors (first day: 23 mmHg (IQR 16–31) vs. 29 mmHg (IQR 25–31), P = 0.029 survivors vs. non-survivors; last day: 22 mmHg (IQR 16–26) vs. 31 mmHg (IQR 23–34), P = 0.043 survivors vs. non-survivors, Figure 5D).

Discussion

The main messages of this retrospective analysis of long-term continuous measurements of right ventricular and ePAD pressures in 30 patients with severe COVID-19 ARDS are as follows:

1 Median RVSPs were substantial and significantly higher on the first day as well on the last day of our long-term measurements in the non-survivors compared with the survivors.

2 Following administration of pulmonary vasodilators, we found a significant decrease in RVSP over time in the
survivors but not in the non-survivors. In addition, within the survivors, we identified also four patients with excessive (e.g. 57–105 mmHg) high RVSPs over several days to weeks, which probably could be lowered successfully by sildenafil in combination with inhaled nitric oxide and inhaled iloprost and which otherwise in all likelihood would have been remained undetected.

At the end of the measurement period, median RVPAMPL was 7 mmHg higher in the non-survivors compared with the survivors indicating substantial right ventricular strain.
4 Compared with the survivors, median ePAD was already 6 mmHg higher in the non-survivors at the first measurement day and increased to 9 mmHg on the last measurement day probably indicating some degree of left heart insufficiency.

Our findings encourage recent results from selective echocardiographic studies, that an estimated sPAP above 35 mmHg carries a seven-fold increased risk of death in patients with severe COVID-19 and acute PAH. In a further echocardiographic study, around 66% of mechanically ventilated COVID-19 patients showed abnormal right ventricular function. Finally, studies in 21 patients with Covid-19 induced ARDS with short-term selective pulmonary artery catheterization found an mPAP of 31 mmHg in non-survivors compared to 25 mmHg in the survivors. Because the relationship between the systolic, mean, and diastolic components of pulmonary artery pressure remains constant under all conditions in both health and disease, and the RVSP equals pulmonary artery systolic pressure in the absence of pulmonic stenosis, our findings of excessive acute right ventricular and thus pulmonary hypertension over days and weeks are clearly clinically relevant in view of the relationship of a substantially increased mortality with PAH in patients suffering from COVID-19 with ARDS.

Our data are the first continuous long-term (up to 30 days) registration of right ventricular pressures in COVID-19 patients with severe ARDS. This continuous registration of RVSP is of special interest because discontinuous tools like transthoracic echocardiography substantially depend on the expertise of the provider underestimating in 60% of patients with PAH the true right ventricular and pulmonary artery systolic pressure measured by right heart catherization. Likewise, insertion of a pulmonary artery catheter is no option because the catheter might induce a wide range of complications (symptomatic disturbances of heart rhythm during insertion, thrombosis of the used vein, infection of the insertion side and/or the catheter, endocarditis, obstruction of a small pulmonary artery with consecutive infarction of the lung, and rarely pulmonary artery rupture by the balloon at the tip of the catheter) and therefore can only be in place for few days. Thus, insertion of an ultrathin probe into the right ventricle seems to be the only way of continuous long-term monitoring of right ventricular and pulmonary artery pressures for reliable detection and treatment of right ventricular hypertension and PAH.

Because impaired right ventricular function along with right ventricular hypertension and PAH measured by echocardiography are prognostic factors for a poor outcome in COVID-19 patients, continuous monitoring of both pressures seems mandatory for decision making and evaluation of treatments. For example, in 16/22 and 7/8 in the survivors and non-survivors, respectively, increases in right ventricular pressures above 40 mmHg in the course of the COVID-19 ARDS have been treated by the pulmonary vasodilator sildenafil alone or in combination with inhaled iloprost or nitric oxide. Consecutively RVSP in the survivors decreased significantly over time but increased non-significantly in non-survivors despite this medication. We would not have acted with pulmonary vasodilators without the continuous measurement of the right ventricular pressure. On the other hand, long-term continuous measurement of RVSP allowed us not to intervene in six patients (five survivors/one non-survivor) with RVSP below 40 mmHg therefore avoiding a probably unnecessary therapy.

An ePAD above 23 mmHg has been shown to be a sensitive indicator not only for acute decompensation but also for long-term mortality in patients with heart failure. In our surviving patients, the initial median ePAD was 23 mmHg and did not change over time suggesting the absence of relevant heart failure. In contrast, the initial median ePADs in the non-survivors were 29 and 31 mmHg at the end of our measurements, with 5/8 patients far above 23 mmHg indicating some degree of left heart failure. In all five patients, transthoracic echocardiography showed depressed left ventricular ejection fraction below 40%. Nevertheless, this conclusion has to be interpreted with caution. First, the number of patients is small, and as mentioned earlier, increase or decrease of ePAD might depend on other factors like volume status or use of vasodilators or vasopressors. Second, the presence of pulmonary thromboembolism (PTE, n = 4 in the survivors, n = 1 in the non-survivors) might also have been disturbed the reliability of ePAD measurements in our patients. To account for that, we undertook a separate analysis excluding all patients with PTE. The results of that analysis with 18 survivors/7 non-survivors were not different to the original data set with 22 survivors/8 non-survivors, suggesting a minor effect of PTE if present at all. Finally, both the survivors and the non-survivors are showing considerable fluctuations over time making identification of trends in ePAD within the presented up to 30 days measurement period sometimes difficult (Figure 4A,B).

The strength of our retrospective analysis is the duration of continuous measurement of right ventricular pressures and thus also of the ePAD. To our knowledge, our data are the first long-term registration of right ventricular pressure dynamics in COVID-19 patients with severe ARDS, showing that more than 4/5 of patients with COVID-19 ARDS developed right ventricular hypertension and thus PAH in the course of the disease. We do not know whether our intervention with pulmonary vasodilators was the only reason for the decrease in right ventricular pressure, because there have been a lot of interventions necessary in the course of the treatment of such patients—infusion control (30/30 patients), intravenous volume reduction by dialysis (12/20 in the survivors and 8/8 in the non-survivors), and veno-venous ECMO (17/20 in the survivors and 7/8 in the non-survivors). Nevertheless, continuous monitoring of right ventricular pressure as measured by the proposed wireless intracardiac pressure transducer 5219 can provide an important new tool for patients and intensive care units.
and estimated pulmonary artery pressure enabled us to treat the right ventricle as prognostic relevant target at least in those patients with a high risk of mortality.2,17,18 Finally, with respect to the so called ‘Long-Covid’ syndrome,22,23 our results might be of interest because the development of right ventricular hypertension and PAH might in part explain the persistence of decreased exercise capacity in patients having survived severe COVID-19 ARDS.

The main weakness of our analysis is the retrospective design without controls. Therefore, the present analysis should be taken as hypothesis generating with the necessity of confirmation in a randomized controlled intervention study in patients with COVID-19 ARDS. In addition, in 9/30 patients, there were missing data over the range of several hours because of decoupling of the connection between the probe and the app. This problem has been solved in the meantime resulting in stable data acquisition up to 30 days.

Finally, extension of continuous bedside monitoring beyond pressures is possible. For example, estimation of right ventricular ejection fraction based on right ventricular pressure measurements seems possible thus coming to a volume based estimation of right ventricular function.24,25 In addition, because continuous long-term monitoring of ePAD as a diagnostic and therapeutic target in heart insufficiency has been shown to reduce hospitalizations as well as mortality,20,21,26,27 a simple and reliable long-term (>1 year) tool for right ventricular and ePAD pressure monitoring with online remote control of changes in haemodynamics might substantially improve the outcomes of patients with acute and chronic left heart failure.

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Conflict of interest
M. Gaertner has no conflict of interest. F. Glocker, R. Glocker, and H.-B. Hopf are shareholders of EMKA Medical GmbH.

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Declaration of Helsinki
This study complies with the Declaration of Helsinki and was approved by the ethics committee of Landesärztekammer Hessen (file No. 2021-2415-evBO). Informed consent of all patients or their next relative was obtained.

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