Right Ventricular Unloading after Initiation of Venovenous Extracorporeal Membrane Oxygenation

To the Editor:

Pulmonary hypertension frequently complicates acute respiratory distress syndrome (1), related to high airway pressures (2), hypoxia, and hypercapnia (3, 4). Venovenous extracorporeal membrane oxygenation (ECMO) improves oxygenation and reduces hypercapnia, facilitating lower airway pressures, and could thus decrease pulmonary hypertension and reduce right ventricular afterload. We therefore studied the effect of initiating venovenous ECMO on mean pulmonary artery pressure (mPAP), cardiac index (CI), and mixed venous oxygenation ($S\bar{v}_{O_2}$).

Thirteen consecutive patients admitted to the Erasmus MC with acute respiratory failure treated with venovenous ECMO were included and studied for the first 6 hours after initiation. Before cannulation, a pulmonary artery catheter (777HF8; Edwards, Irvine, CA) was inserted. Heart rate, mean arterial pressures, peripheral oxygenation, mPAP, and CI were recorded just before initiation of venovenous ECMO (baseline) and at 30 seconds as well as 1, 3, 5, 10, and 15 minutes and 1 and 6 hours after initiation of venovenous ECMO. CI was measured continuously (Vigilance II monitor; Edwards). In six patients, $S\bar{v}_{O_2}$ measurements were available.

All parameters were normally distributed. The effects of venovenous ECMO on hemodynamics and $S\bar{v}_{O_2}$ at each point were tested, using generalized estimating equations in all patients, at all points, with the baseline values as covariates. The association between mPAP and $S\bar{v}_{O_2}$ was tested with generalized estimating equations in six patients during the first 15 minutes. Values of the first blood gas after initiation of venovenous ECMO were subtracted from the values of the last blood gas analysis before venovenous ECMO and were defined as "Δ." The associations among ΔPa_{O_2}, ΔPa_{CO_2}, and ΔmPAP were analyzed using Pearson's correlation coefficient. All data are expressed in mean ± SE unless otherwise stated.

Eleven men and two women (age, 58 ± 3 yr) were included. All patients were diagnosed with pneumonia (seven bacterial, five viral, and one culture negative). Two patients were on the waiting list for lung transplantation. Baseline mPAP of these chronic patients was 26 and 43 mm Hg before initiation of venovenous ECMO. Three patients were treated with the Quadrox PLS oxygenator (Maquet, Rastatt, Germany); the others were treated with an iLa-Active system (6 XLung oxygenator and 4 NovaLung oxygenator; NovaLung, Heilbron, Germany). The NovaLung oxygenator does not have a heater, as the priming volume is low. In all other systems, ECMO blood flow was heated to 37°C. One patient received a jugular 31-Fr double lumen cannula; all others received a 25- or 29-Fr femoral cannula with a 19- or 21-Fr reinfusion jugular cannula.

Table 1. Baseline Characteristics and Values after Initiation of Venovenous Extracorporeal Membrane Oxygenation

		Time after Initiation Venovenous Extracorporeal Membrane Oxygenation (*min*)							
	Baseline	**0.5**	**1**	**3**	**5**	**10**	**15**	**60**	**720**
PIP, mbar	35 ± 2	35 ± 2	35 ± 2	29 ± 2	29 ± 2	25 ± 2	24 ± 2	22 ± 1	24 ± 1
PEEP, mbar	16 ± 2	16 ± 2	15 ± 2	14 ± 2	15 ± 2	15 ± 2	14 ± 2	14 ± 1	14 ± 1
VT/PBW, ml/kg	6.6 ± 0.7	6.6 ± 0.7	6.4 ± 0.7	6.3 ± 0.7	5.6 ± 0.8	4.5 ± 0.6	4.5 ± 0.6	3.5 ± 0.4	3.2 ± 0.4
MPaw, mbar	24 ± 2	24 ± 2	23 ± 2	21 ± 2	21 ± 2	20 ± 2	19 ± 2	17 ± 1	19 ± 1
$F_{I_{O_2}}$, %	85 ± 4	85 ± 4	85 ± 4	76 ± 6	72 ± 6	63 ± 6	60 ± 6	45 ± 3	40 ± 3
pH	7.2 ± 0.3						7.3 ± 0.4	7.3 ± 0.2	7.3 ± 0.3
Pa_{O_2}, mm Hg	94 ± 15						127 ± 27	104 ± 11	88 ± 6
Pa_{CO_2}, mm Hg	65 ± 5						53 ± 8	48 ± 4	47 ± 3
HR, beats/min	114 ± 6	111 ± 5*	109 ± 5*	111 ± 6*	109 ± 6*	107 ± 8*	106 ± 7*	104 ± 7*	95 ± 6*
MAP, mm Hg	68 ± 4	64 ± 4*	63 ± 5*	70 ± 5	78 ± 5*	72 ± 6*	69 ± 5	75 ± 4	74 ± 4
mPAP, mm Hg	40 ± 3	38 ± 3*	37 ± 3*	36 ± 3*	35 ± 3*	32 ± 4*	32 ± 3*	34 ± 2*	33 ± 2*
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	3.0 ± 0.3	3.2 ± 0.4	2.7 ± 0.3	2.9 ± 0.3	3.2 ± 0.3	3.2 ± 0.4*	3.1 ± 0.2	3.5 ± 0.4	3.4 ± 0.3
CVP, mm Hg	15 ± 2	15 ± 2	15 ± 2	14 ± 2	13 ± 2	12 ± 3	12 ± 2*	14 ± 2	15 ± 3

Definition of abbreviations: CVP = central venous pressure; $F_{I_{O_2}}$ = inspired oxygen fraction (on mechanical ventilator); HR = heart rate; MAP = mean arterial pressure; mPAP = mean pulmonary artery pressure; MPaw = mean airway pressure; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; VT/PBW = tidal volume divided by predicted body weight.
Mean ± SE.
*$P < 0.05$ compared with before initiation of venovenous extracorporeal membrane oxygenation (baseline).

Before initiation of venovenous ECMO, mPAP was 40 ± 3 mm Hg (range, 26–56 mm Hg). Mean ECMO blood flow at the end of the study was 4.6 ± 0.9 L/min (*see* Figure E1 in the online supplement for individual ECMO blood flow over time). Already, 30 seconds after initiating venovenous ECMO, mPAP started to decrease (mean change over all points, −4.7 ± 0.5 mm Hg; $P <$ 0.05) (Table 1). The change in mPAP was significantly associated

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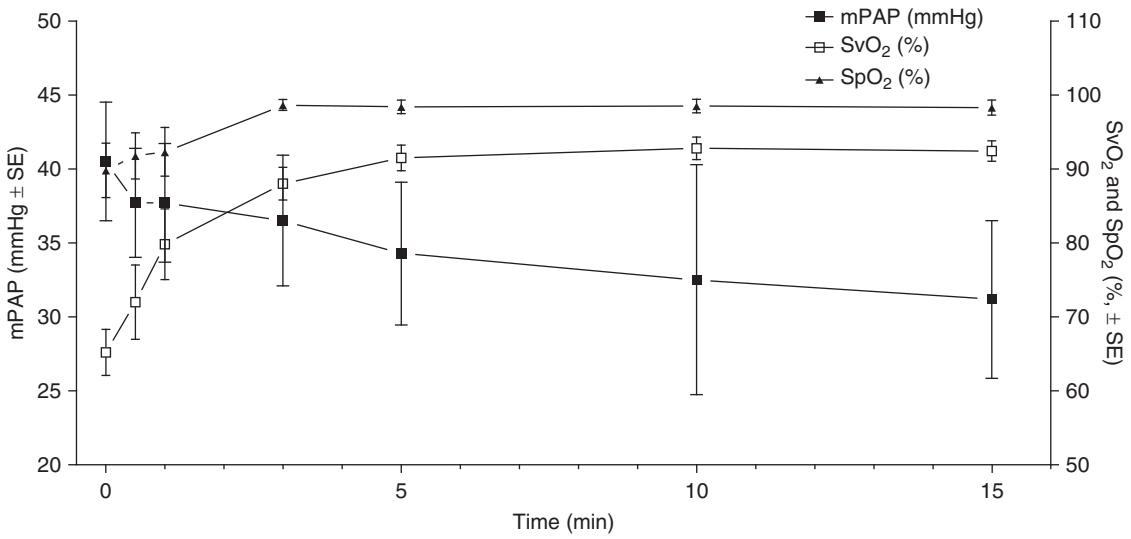

Figure 1. Mean pulmonary artery pressure (mPAP) and oxygen saturation in the pulmonary artery ($S\bar{v}_{O_2}$) versus time after initiation of venovenous extracorporeal membrane oxygenation in six patients in whom $S\bar{v}_{O_2}$ was available. Mean ± SE. Sp_{O_2} = peripheral oxygen saturation.

with a decrease in Pa_{CO_2} and an increase in $S\bar{v}_{O_2}$ (Figure 1; Figure E2 depicts relative changes from baseline in mPAP and $S\bar{v}_{O_2}$). CI increased and central venous pressure decreased significantly after initiation of venovenous ECMO (Table 1). No significant association was found among mPAP, Pa_{O_2}, or peripheral oxygenation. Vasopressor use did not change over time. The fluid balance in the first hour after initiation of venovenous ECMO was 206 ± 105 ml positive (740 ± 194 ml during the 6-hour study period). Four patients received blood products during the study period (five packed cells, two fresh frozen plasma, and three units of thrombocytes in total).

In this study, we found that initiation of venovenous ECMO resulted in a reduction of right ventricular afterload that was associated with an immediate decrease in mPAP associated with a significant, but not clinically relevant, increase in CI, a decrease in central venous pressure, and an increase in $S\bar{v}_{O_2}$. In addition, Pa_{CO_2} decreased significantly after the initiation of venovenous ECMO.

Hypoxic pulmonary vasoconstriction is mostly mediated in the precapillary arterioles (5) and could therefore explain the immediate decrease in mPAP associated with the rise in $S\bar{v}_{O_2}$. In addition, the decrease in Pa_{CO_2} after the start of venovenous ECMO could also have contributed to the decrease in mPAP (4). Schmidt and colleagues (6) studied the effect of changing sweep gas flow over the ECMO oxygenator in patients receiving venovenous ECMO, reporting a decrease in Pa_{CO_2} associated with a significant reduction in mPAP.

Immediately after initiation of venovenous ECMO, the right ventricle is off-loaded by an immediate decrease in mPAP. Therefore, the presence of pulmonary hypertension in patients with severe acute respiratory distress syndrome may not be a contraindication for venovenous ECMO, as this may even alleviate right ventricular dysfunction/failure related to the pulmonary hypertension. A limitation of this study is that CI was measured by thermodilution. Part of the thermal signal could be lost in the venovenous ECMO flow when part of the PA catheter's thermal filament was situated in the right atrium. However, we did not observe unexpected changes in CI using the fast updating CI measurements (30- to 60-s sampling interval) directly after initiation of venovenous ECMO. In addition, the timing of changes in ventilator settings after initiation of venovenous ECMO varied in this observational study, which might have caused variability in Pa_{O_2}, possibly explaining the lack of correlation between mPAP and Pa_{O_2}.

In conclusion, initiation of venovenous ECMO in respiratory failure is associated with immediate right ventricular unloading associated with an increase in $S\bar{v}_{O_2}$ and a decrease in Pa_{CO_2}. ■

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Fungus-Specific CD4$^+$ T Cells for Rapid Identification of Invasive Pulmonary Mold Infection

To the Editor:

Invasive mold infections (IMIs) are difficult to diagnose in immunocompromised patients, resulting in substantial mortality of up to 100% in untreated IMIs (1). Early initiation of targeted antifungal therapy is key for improving prognosis (2, 3), but specific and reliable noninvasive diagnostic methods are lacking. At this time, combinations of host risk factors, imaging studies, signs and symptoms, and galactomannan testing result in a working hypothesis of probable or possible IMI (4). The diagnostic gold standard is histologic proof of infection or cultural growth from tissue biopsy (4, 5). Frequently, tissue cannot be obtained, as in the vast majority of high-risk patients, surgical procedures are contraindicated. Moreover, histological examination does not reliably differentiate between fungal genera and species, and fungal growth in culture often remains unsuccessful (6, 7). Here we applied a different approach to identifying IMI by using the patient's fungus-specific T cells as a diagnostic read-out. We previously showed that the total pool of conventional antigen-reactive CD4$^+$ T cells can be detected with high specificity and sensitivity, based on the upregulation of CD154 (CD40L), following brief *in vitro* stimulation with fungal antigens (8–10). We use this sensitive technology to monitor mold-reactive CD154$^+$ T cells by flow cytometry in peripheral blood of hematological patients at risk for or with established diagnosis of IMI.

In a control cohort of 100 healthy donors, the mean proportions of *Aspergillus* spp. and Mucorales-reactive CD4$^+$ lymphocytes were 0.14% ± 0.07%, and 0.06% ± 0.03%, respectively (Figure 1A). Compared with healthy control patients, all but one patient with proven IMI had markedly increased frequencies of mold-reactive CD4$^+$ cells (Figure 1A). Whenever possible, we monitored frequencies in these patients at several points. Despite some variability during longitudinal assessment, mold-reactive CD4$^+$ T-cell frequencies were generally higher than in healthy control patients. A cut-off value allowing discrimination between infected and noninfected individuals was determined by receiver-operating characteristic analysis of healthy donors and patients with proven IMI, as only this patient group has a reliable diagnosis of IMI (*see* Figure E1 in the online supplement). The derived cut-offs were 0.39% CD154$^+$ cells among CD4$^+$ lymphocytes for *Aspergillus* spp. and 0.16% for Mucorales, respectively. Of 20 hematologic patients at risk, but without clinical signs or symptoms of disease ("no IMI"), only one patient displayed increased frequencies at a single point. Also, in 20 (69%) of 29 patients with possible IMI, T-cell frequencies were not increased. The remaining 9 (31%) patients with possible IMI displayed strongly increased T-cell frequencies, mostly at several points, suggesting the presence of IMI (Figure 1A). Whereas elevated T-cell frequencies remained high during the course of proven IMI, elevated frequencies of Mucorales-reactive CD4$^+$ T cells rapidly dropped in four patients after surgical resection of the infected tissue (Figure 1B), suggesting that increased frequencies result from acute antigen stimulation, and thus represent a potential marker for ongoing IMI.

Although clinical suspicion, for example, possible or probable IMI, may serve as a surrogate for treatment initiation, proof of IMI remains elusive without biopsy (4). To determine the sensitivity and specificity of our assay, T-cell frequencies of patients with histologically proven IMIs were compared with patients without proof of IMI. Nine of 10 patients with proven IMI displayed increased T-cell frequencies, and in 39 of 49 patients without proven IMI, frequencies were normal, resulting in a sensitivity of 90% and a specificity of 80%. Positive and negative predictive values were 28 and 99%, respectively. Comparison of positive and negative T-cell signals and the clinical European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group classification (4) showed a statistically significant correlation of clinical diagnosis of IMI with mold-reactive CD4$^+$ lymphocyte frequencies ($P < 0.0001$). One patient with proven IMI had a false-negative T-cell signal. In this case, only a single measurement was performed. Repeated measurements may enhance sensitivity in future analyses. Ten patients at risk for IMI, but without proven infection, had increased mold-reactive T-cell frequencies. These formally false-positive test results coincided with clinical suspicion of IMI, as nine of these

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