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Continuous gas transfer monitoring during extracorporeal membrane oxygenation

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ABSTRACT

Extracorporeal membrane oxygenation therapy can prevent hypoxia, and the related inherent danger of death, if mechanical ventilation does not maintain sufficient physiological gas exchange. This form of therapy provides supplemental extracorporeal blood oxygenation and decarboxylation. The most important values to be monitored for the supervision of extracorporeal gas exchange are blood gas measurements, which are normally obtained only intermittently. Continuous measurement during this therapy is rarely implemented because the devices used are costly, and the amount of supervision and maintenance required is complex and expensive (even on the relatively short term of several hours). We present an alternative approach to supervise extracorporeal gas exchange that avoids the use of blood gas analyzers. This is achieved using venous oxygen saturation and additional sensors within the gas phase of the extracorporeal setup. Finally, carbon dioxide gas transfer is measured directly and oxygen gas transfer is estimated using an extended Kalman filter based on an evaluated gray-box model. The proposed method is characterized *in silico* and evaluated using *in vivo* data (accuracy of oxygen gas transfer estimation 9.1 ± 49 mL/min). Results suggest that monitoring of gas transfer with adequate performance is possible and that clinical application using this measurement value in closed-loop control is also feasible.

1. Introduction[1]

The use of extracorporeal membrane oxygenation (ECMO) alone can keep a patient alive if, despite mechanical ventilation, sufficient pulmonary gas exchange is no longer possible. Pulmonary gas exchange is impaired if oxygen (O_2) supply and carbon dioxide (CO_2) removal, or both, do not satisfy the physiological needs of the patient [2]. This situation may arise in case of acute respiratory distress syndrome (ARDS), acute respiratory failure, chronic obstructive pulmonary disease, pneumonia or preterm birth [3–5]. In addition, ECMO therapy can reduce the strain resulting from mechanical ventilation by increasing extracorporeal gas transfer, which may prevent or inhibit ventilator-induced lung injury [6] and may improve outcome [7–9]. The Extracorporeal Life Support Organization has reported that ≥69,000 patients worldwide have received ECMO therapy over the last 24 years, of which 59% have survived up to discharge or transfer [3].

During ECMO therapy, circulation is extended outside the body using large cannulas (e.g. 20 French). The blood flow Q_b is often maintained by a pump and passes through an oxygenator. At the same time, the oxygenator is fed with a mixture of O_2 and nitrogen (N_2) by means of a gas mixer. Finally, O_2 and CO_2 diffuse through a thin semipermeable membrane, which separates gas and blood phases.

In practice, knowledge of gas partial pressures in blood ($p_{O_2,b}$ and $p_{CO_2,b}$) is necessary to assess the states of the oxygenator and to control oxygenation and CO_2 removal. However, such measurements are invasive, costly (when applied continuously) and only possible for a limited period of time (continuously up to several hours). Therefore, we aim to measure concentrations on the gas side (which is known to be reliable, durable and efficient) and calculate blood gas transfer (Q_{O_2} and Q_{CO_2}) from these data to replace the $p_{O_2,b}$ and $p_{CO_2,b}$ measurements. In order to achieve this, however, a particular challenge is the modeling of the varying time delays and the non-linear O_2 absorption of blood.

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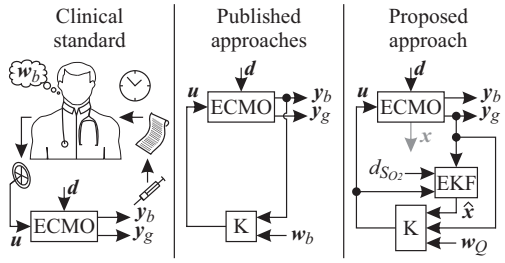

Fig. 1. Comparison of approaches to control ECMO therapy, which is adjusted by the set values $\boldsymbol{u}$ and affected by the disturbances $\boldsymbol{d}$. In the first two cases the desired values $\boldsymbol{w}_b$ are evaluated using invasive BGA measurements, which are not needed in the proposed approach. *Left panel*: usually, medical experts adjust ECMO therapy manually. *Center panel*: a control system K continuously optimizes the ECMO therapy. *Right panel*: the control loop includes a control system K to adjust the desired gas transfer rates $\boldsymbol{w}_Q$ and an extended Kalman filter (EKF) which estimates process states $\hat{\boldsymbol{x}}$ (placing a hat over a true parameter denotes an estimator of it, e.g., $\hat{\boldsymbol{x}}$ is an estimator for $\boldsymbol{x}$) using $\boldsymbol{u}$, $\boldsymbol{y}_g$ and $d_{S_{O_2}}$.

1.1. State of the art

Shekar et al. offer detailed insight into the commercially available ECMO systems [10]. With the exception of the Hemolung™ system (Alung Technologies, Pittsburgh, PA, USA), most systems do not quantify gas transfer. The Hemolung™ provides extracorporeal CO_2 removal at small Q_b below 0.55 L/min and displays the CO_2 removal in mL/min in real-time as well as over time. For this, the mass flow and the CO_2 fraction of the gas are measured and multiplied after flowing through the oxygenator. Normally, the extracorporeal O_2 gas transfer rate Q_{O_2} is calculated based on blood values obtained from the blood gas analyzer (BGA) both before and after the oxygenator. Until now, in clinical practice the Q_{O_2} has received little attention. This is in contrast to its role in various research projects: in particular, when hollow fibers or oxygenators are characterized under controlled laboratory conditions [11,12], or, for example, when different oxygenators are compared [13].

Nowadays, ECMO therapy is still intermittently set by medical experts (Fig. 1, left panel), who select the set values $\boldsymbol{u}$ based on their expertise, and on BGA values and laboratory reports. It is maintained up to several weeks in the intensive care unit. In the case of such long-term therapy, supervision is generally intermittent due to limited personnel resources [14]. Automation of ECMO therapy is currently the aim of various research projects [14–16]. Similar developments have taken place in heart-lung machine systems [17–20]. The published ECMO therapy control systems (Fig. 1, center panel) use BGAs (measuring for example $p_{O_2,b}$, $p_{CO_2,b}$ and pH), which include extra bypasses with additional pumps in the extracorporeal circuit (CDI® Blood Parameter Monitoring System 500; Terumo Cardiovascular Systems Corporation, Ann Arbor, MI, USA) or slow sampling (analysis time to measurement result 3 min: Proxima, Sphere Medical Ltd., Cambridge, UK) [18]. That automated ECMO therapy is not yet used in daily practice is probably because continuous measurements in blood are both complex and risky.

To overcome these drawbacks, we present continuous and non-invasive methods to measure extracorporeal gas transfer rates Q_{O_2} and Q_{CO_2} during EMCO therapy, which might replace the invasive BGA measurements or can be used in a control loop (Fig. 1, right panel). In this case, Q_{O_2} and Q_{CO_2} are non-invasively calculated based on the estimated process states ($\hat{\boldsymbol{x}}$), non-invasive measurements in the gas phase ($\boldsymbol{y}_g$) and the O_2 saturation at the oxygenator blood inlet ($d_{S_{O_2}}$). The latter can be easily measured using optical inline measurement systems which are integrated in most commonly used ECMO systems (Cardiohelp-i, Maquet GmbH & Co. KG, 76437 Rastatt, Germany).

Table 1
Comparison of continuous gas transfer monitoring system properties of the proposed gas phase based approach and the BGA based measurement using the CDI® system [1].

Property	BGA-based	Gas phase-based
Long-term stability	Poor	Present
Calibration	Required before usage	Not needed
Dynamic response	Slow	Fast
Durability	Limited	Not limited
Disposables	Complex and expensive	Ordinary and inexpensive
Blood contact and -carrying bypasses	Present	Not present

1.2. Gas transfer monitoring

Based on measurements in the gas phase, gas transfer monitoring enables to observe and supervise the ECMO without a BGA. For that purpose, a mass flow sensor (AWM5104VC; Honeywell, Freeport, IL, USA) was integrated into the gas carrying tube next to the oxygenator gas inlet and two anesthetic gas monitors of the Primus® anesthesia workstation (Dräger Medical GmbH, Lübeck, Germany) were added close to the gas inlet and outlet of the oxygenator. The anesthetic gas monitors measure (amongst other parameters) O_2 and CO_2 fractions of the ECMO gas mixtures. The CO_2 transfer rate Q_{CO_2} is calculated by multiplying the CO_2 fraction $F_{CO_2,out}$ and the gas flow Q_g, similar to the Hemolung™ system. Concerning O_2, using the proposed extended Kalman filter, the resulting $\hat{Q}_{O_2}$ between blood and gas in the oxygenator can be estimated with sufficient accuracy. The input values included are: O_2 fraction $F_{O_2,in}$, gas flow Q_g and blood flow Q_b (measured at the oxygenator inlets) and the inline measured venous O_2 saturation $S_{O_2,ven}$. The filter is based on a previous published nonlinear gray-box model of the oxygenator, which was evaluated using BGAs [14,21]. Finally, the missing output, which acquires the fraction of O_2 at the gas outlet, was added to the model.

In addition, gas transfer estimation based on anesthetic gas monitors overcomes all the weaknesses and drawbacks associated with BGA-based ECMO therapy monitoring. For instance, selected properties of the CDI® Blood Parameter Monitoring System 500 with shunt sensors are compared with the properties of commercially available anesthetic gas monitors, mass flow sensors and optical inline measurement systems for ECMO (Table 1).

Furthermore, anesthetic gas monitors are standard measurement systems in intensive care units (e.g. as part of a ventilator or an anesthesia workstation). Also, optical S_{O_2} inline measurement systems for ECMO are already integrated into available ECMO systems.

2. Material and methods

2.1. Experimental setup

The experimental setup for testing the proposed approach was approved by the relevant animal welfare authority (84-02.04.2014.A113; LANUV NRW, Postfach 101052, 45610 Recklinghausen, Germany). The subject was a fully anesthetized, monitored and mechanically ventilated female midi-pig (approx. 60 kg) with an artificially introduced lung injury [22]. The extracorporeal system was equivalent to a veno-venous ECMO setup: venous blood is taken from both femoral veins with large-lumen tubes (18–21 French), pumped through an oxygenator, and returned with one large-lumen tube into the jugular vein. In this case, two femoral tubes are used to reduce the risk of cannula occlusion.