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Closed-loop control of extracorporeal oxygen and carbon dioxide gas transfer

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ABSTRACT

Additional extracorporeal gas transfer facilitates ultra-protective mechanical ventilation during treatment of severe lung disease. The proposed automation contributes to both patient safety and therapeutic success. A decentralized control system set the oxygen and carbon dioxide gas transfer rates. The controlled variables are estimated using standard measurement devices without direct blood contact. To reduce patient stress, an outer-loop integral controller adjusts the extracorporeal blood flow. The control system was first evaluated *in silico* and then *in vivo* using an animal model. Finally, the method is shown to be feasible and its response time is sufficient to meet patients' clinical needs.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) therapy is nowadays used as a last resort to rescue patients [e.g. in case of severe acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease, pneumonia or restrictive lung disorder], when mechanical ventilation (MV) is no longer sufficient. This implies that the necessary oxygen (O_2) and carbon dioxide (CO_2) gas exchange with the environment remain below the patient's physiological needs, possibly leading to ventilator-induced lung injury (VILI). However, in these cases, changing the settings of MV (e.g. tidal volume) to allow additional pulmonary gas transfer may cause additional stress and strain on the lung; this is in conflict with the aim to achieve effective recovery of the diseased lung. Therefore, only application of an ECMO system provides the additional O_2 and CO_2 gas exchange that is required to relieve the stress introduced by MV (Chiumello et al., 2008; Sangalli, Patroniti, & Pesenti, 2014; Schmidt et al., 2014; Siebert, 2010).

1.1. Extracorporeal membrane oxygenation

ECMO therapy was first applied to a human in 1972 (Hill et al., 1972). Meanwhile, in 2015 the Extracorporeal Life Support Organization reported that, of the ≥65, 000 patients who received ECMO therapy during the last 24 years, only 59 % survived up to discharge or transfer (Extracorporeal Life Support Organization, 2015). However, continuous developments over the last decades have reduced mortality (a drop of about 30 % between 1970 and 2000) (Lewandowski, 2000), and a randomized trial showed that the sixth-month survival rate of ARDS patients was approx. 15% higher using modern ECMO therapy compared to conventional MV (Peek et al., 2010). Also, during the H1N1 pandemic in 2009, ECMO therapy improved the outcome by enabling ultra-protective MV (Noah et al., 2011; Pham et al., 2013).

The main objective of ECMO therapy is to keep physiological values (e.g. venous CO_2 partial pressure $p_{CO_2,ven}$ and peripheral O_2 saturation $S_{O_2,p}$) within defined limits. For this purpose, the extracorporeal setup transfers O_2 (with the rate Q_{O_2}) into the patient's blood and eliminates CO_2 (with the rate Q_{CO_2}) from it.

The basic design of the therapy is presented in Fig. 1. Circulation is extended outside the patient's body using tubes and a pump, which adjusts the blood flow rate Q_b. The withdrawn blood enters the oxygenator and is characterized by its O_2 saturation $S_{O_2,in}$, O_2 partial pressure $p_{O_2,in}$ and CO_2 partial pressure $p_{CO_2,in}$. At the same time, a gas blender provides a mixture of O_2 and nitrogen (N_2) to adjust the O_2 fraction $F_{O_2,g,in}$. Subsequently, the blended gas flushes the oxygenator with the flow rate $Q_{g,in}$. In the oxygenator, blood and gas are separated by a thin ($d \approx 90\,\mu m$), extensive ($A \approx 2\,m^2$) and semipermeable membrane: O_2 and CO_2 diffuse through the membrane due to differences in

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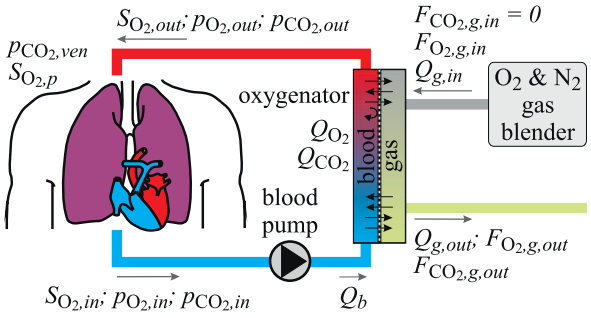

Fig. 1. Components and state variables of ECMO therapy.

partial pressure between blood and gas, in accordance with Fick's first law. Thus, the composition of the gas changes in the oxygenator and the gas flow leaving the oxygenator is characterized by the rate $Q_{g,out}$, the O_2 fraction $F_{O_2,g,out}$ and the CO_2 fraction $F_{CO_2,g,out}$. Also, in the oxygenator, blood gas values change (p_{CO_2} decreases, p_{O_2} increases, and S_{O_2} increases) due to O_2 and CO_2 gas transfer. Finally, the blood is oxygenated, decarbonized and fed back into the patient's circulation.

The presented control loop is designed using a veno-venous ECMO setup: blood is withdrawn from and fed back into large venous vessels. This means that high blood flow rates are possible and withdrawn blood is characterized by a low O_2 and high CO_2 content. This enables to provide high extracorporeal O_2 and CO_2 gas transfer rates without puncturing an arterial vessel.

Currently, during a patient's (generally short-term) stay on the intensive care unit (ICU), healthcare staff only intermittently adjust ECMO settings in accordance with general guidelines (e.g. $Q_b = 30$–$50\,\%$ of cardiac output, $F_{O_2,g,in} = 100\,\%$) (Bensberg, Dembinski, Kopp, & Kuhlen, 2005; Shekar et al., 2014). However, in the case of long-term therapy (e.g. perhaps for weeks) continuous supervision on the ICU is impossible due to limited staff/resources. Therefore, currently, it is not possible to support continuous intra- and inter-individual optimization of ECMO therapy.

To overcome this drawback various groups have investigated automation of extracorporeal circulation (Mendoza García et al., 2014; Misgeld, Werner, & Hexamer, 2010; Smith & Porumamilla, 2011; Walter, Brendle et al., 2011; Walter, Wartzek et al., 2009). Generally, these systems use blood gas values (e.g. partial pressure) as control variables. However, the required continuous blood gas analysis (BGA) systems are characterized by slow dynamics and their practical applicability is rather limited (Brendle et al., 2015; Hexamer & Werner, 2003). An alternative approach is to utilize the extracorporeal O_2 and CO_2 gas transfer rates as control variables. These internal oxygenator states can be supervised using anesthesia gas monitors (AGMs) and inline measured $S_{O_2,in}$ combined with an extended Kalman filter (Brendle et al., 2015). In the following, the first approach to control these estimated gas transfer rates is presented.

1.2. Objective for gas transfer control

Usually, individual therapy optimization is only performed in irregular care intervals, which can be suboptimal due to changes of the patient's constitution (e.g. by improvements of the lung gas transfer ability) or changes in the therapy system (e.g. degradation of the oxygenator). In general, the ECMO settings have to be continuously adjusted to enable optimization of the treatment. For example, a too high blood flow rate might cause patient stress (particularly with regard to hemolysis, hemodynamics, or recirculation) (Kameneva et al., 2004; Zhang et al., 2011). On the other hand, a sufficient level of blood flow is necessary to satisfy inter- and intra-individual O_2 and CO_2 gas transfer demands. However, in current practice, ECMO therapy is still intermittently adjusted by healthcare staff. In addition, until now, no large study has aimed at obtaining approval for automation of ECMO

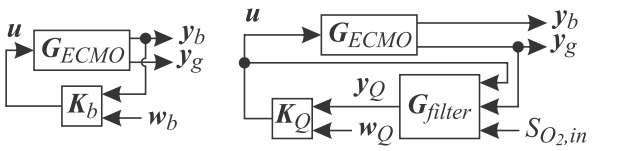

Fig. 2. Left: previously published control systems (controller K_b sets u such that y_b follows given blood gas values w_b) (Mendoza García et al., 2014; Misgeld et al., 2010; Smith & Porumamilla, 2011; Walter, Brendle et al., 2011; Walter, Wartzek et al., 2009). *Right*: the proposed ECMO closed-loop control including the extended Kalman filter G_{filter} and the control system K_Q.

therapy, even though earlier approaches, which control BGA values $\mathbf{y}_b$ at the oxygenator outlet (Fig. 2, left), demonstrated the feasibility and effectiveness of automated therapy in experimental trials. Possible reasons for not obtaining approval include the complexity of handling, associated costs and additional safety risks, which are related to the continuous BGA systems required to measure $\mathbf{y}_b$ (Brendle et al., 2015). Therefore, the earlier approaches appear to have features that make them economically untenable.

This paper presents a different approach (Fig. 2, right), which does not use BGA values $\boldsymbol{y}_b$ (e.g. O_2 and CO_2 partial pressures at the oxygenator outlet). Instead, the O_2 and CO_2 fraction of the sweep gas at the oxygenator outlet $\boldsymbol{y}_g = [F_{O_2,out}, F_{CO_2,out}]^T$, O_2 saturation of the withdrawn blood $S_{O_2,in}$, and the ECMO set points $\boldsymbol{u} = [Q_{b,u}, Q_{g,u}, F_{O_2,g,u}]^T$ (blood flow, gas flow and O_2 fraction) enable the extended Kalman filter $\boldsymbol{G}_{filter}$ to estimate the extracorporeal process variables $\boldsymbol{y}_Q = [\hat{Q}_{CO_2,y}, \hat{Q}_{O_2,y}, \hat{S}_{O_2,out}]^T$ (extracorporeal O_2 and CO_2 gas transfers rates and O_2 saturation of the blood at the oxygenator outlet). Finally, a robust closed-loop control system sets given extracorporeal O_2 and CO_2 gas transfers rates $\boldsymbol{w}_Q = [Q_{CO_2,w}, Q_{O_2,w}]^T$.

For the clinical practice, this approach has the following favorable properties: only standard measuring devices are used that are part of medical products (e.g. AGMs as part of anesthesia equipment, or optical inline S_{O_2} sensors as part of integrated ECMO systems). Moreover, because the sensors are reusable, need few disposables and no specialized maintenance, this makes the system efficient and easy to handle. In addition, the sensors are located in the noncritical gas carrying tubes, have no contact with blood, and require no further circulatory extension of the setup. This implies that patient safety is unimpaired during gas transfer monitoring.

In summary: this method of estimating gas transfer overcomes the practical drawbacks of the earlier automated ECMO systems; moreover, integration is possible into existing ECMO systems. Besides, process control operates without the measurement of partial pressure in blood. In practice, these values are intermittently measured to supervise the ECMO system. In consequence, this approach presents a novel modality to operate ECMO systems, which is not established in daily care.

With regard to the clinical objective, this paper presents a major breakthrough: the gas transfer control system is intended to be used as an inner loop within a cascaded control system for automation of ECMO therapy (Fig. 3). Hereby, extracorporeal blood flow is continuously minimized, depending on the patient's gas transfer demands. This prevents extra/non-essential blood flow (that can cause hemolysis and stress). Furthermore, the extracorporeal gas transfer rates $\boldsymbol{y}_Q$ gain oxygenation and decarbonization of arterial blood. Thus, using $\boldsymbol{w}_Q$ as a

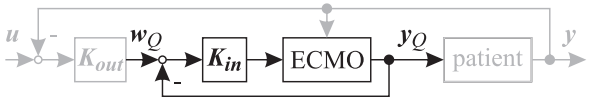

Fig. 3. Cascaded control system for automation of the ECMO therapy. The ECMO gas transfer rate control system (inner loop, *black*) includes the proposed controller K_{in} and the ECMO system, whose gas transfer capacity is co-determined by the patient blood gas values.And the intended future patient in the loop system (outer loop, *gray*) including physiological target controller K_{out}.