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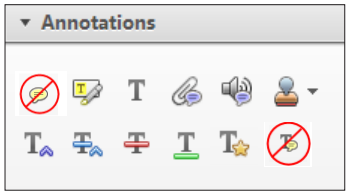

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Cardiac output: a central issue in patients with respiratory extracorporeal support.

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Abstract

The ILA-Activve® Novalung is a new extracorporeal device specifically designed for lung support in patients with hypercapnic and/or hypoxemic respiratory failure. To date, only low-flow applications for decompensated hypercapnic chronic obstructive pulmonary disease have been reported in the literature. Here, we briefly report three cases of iLA-Activve use in patients with hypercapnic-hypoxemia acute lung failure assisted with mid-flow (up to 2.4 L/min) and different single/double venous cannulation. The main findings of our small case series were: firstly, extracorporeal blood flows over 2.0 L/min across the membrane provided clinically satisfying decarboxylation and improved oxygenation; secondly, the ratio between blood flow through the membrane and the patient's cardiac output (CO) was a major determinant for the oxygen increase. The latter could, therefore, be a useful indicator for understanding performance in the complex and multifactorial evaluation of patients with extracorporeal veno-venous lung support.

Keywords

decap; respiratory failure; ECMO; cardiac output; Novalung; iLA-Activve

Introduction

In recent years, thanks to a remarkable increase in knowledge and the development of materials and techniques, extracorporeal respiratory support has become increasingly popular for critically ill patients with severe lung failure.[1,2] Systems with different levels of performance and invasiveness are now available for clinicians who work in intensive care units (ICUs). These range from less invasive devices for extracorporeal carbon dioxide (CO_2) removal ($ECCO_2$-R), to the more invasive extracorporeal membrane oxygenation (ECMO) devices.[3] The iLA-Activve® (International Lung Assist; Novalung, Heilbronn; Germany) – a pump-driven veno-venous (V-V) respiratory support – has recently been developed and delivered onto the market.[4] Here, we briefly report three cases of iLA-Activve® use in patients with acute lung failure, with the aim of discussing the possibility to increase oxygenation and the key role of patients' cardiac output (CO) in the performance of V-V lung assist systems.

Case reports

Table 1 summarizes the arterial blood gas analyses data, patient COs, extracorporeal pump flows and oxygen flows measured in each described case.

1. The first patient was a 63-year-old man (87 kg; 172 cm), admitted to the ICU for acute respiratory failure with a diagnosis of H1N1 infection. Past medical history included congenital inferior

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vena cava (IVC) agenesis, renal transplantation and recent pneumonia due to *Pneumocistis jirovecii* (two months before ICU admission). After the initial 48-hr management with non-invasive positive pressure ventilation (NIPPV), endotracheal intubation became necessary due to the progressive worsening of hypercapnia and hypoxemia (during NIPPV set at FiO_2 100%, PEEP 8 mmHg, PaO_2 was 75 mmHg and $PaCO_2$ 65 mmHg; pH 7.27). After 24 hours of invasive ventilation (IPPV) and despite a reduction in hypercapnia ($PaCO_2$ now at 44.4 mmHg), a decision was made to put the patient on iLA-Activve® extracorporeal support due to the worsening of the refractory hypoxemia (see Table 1, case 1). A double venous cannulation was performed, with the outlet flow (from patient to machine) through a single-lumen 20 Fr catheter placed into the right common femoral vein (Maquet, Rastatt, Germany) and the inlet flow (from machine to patient) through a 16 Fr catheter placed into the right internal jugular vein (OptiSite Edwards Lifesciences, Irvine, CA, USA). Cardiac output was estimated using the MostCare™ system (a pulse contour method that analyzes the arterial pressure waveform – Vygon, Vytech, Padova, Italy),[5] showing a value of 7.2 L/min before lung assist and 6.8 L/min just after (average of data estimated in beat-to-beat manner).[6] With an extracorporeal blood flow of 1.9 L/min, oxygenation increased by 67% and CO_2 decreased by 27%, with 4 L/min O_2 of sweep gas delivered to the artificial lung (iLA membrane) (Table 1 and Figure 1). The patient was successfully weaned off the extracorporeal assistance after 7 days. No device-related complications were observed at any time. Seven days later, a secondary infection due to a multi-drug-resistant *Acinetobacter baumanii* caused a septic shock, leading to death.

2. The second patient was a 69-year-old man with Hodgkin's lymphoma who developed an acute lung failure due to *Klebsiella pneumoniae* respiratory infection. After two weeks of ventilatory support with high-flow oxygen therapy and NIPPV and five days of invasive mechanical ventilation, an extracorporeal respiratory support was implanted for refractory hypoxemic-hypercapnic respiratory failure. As an initial strategy, a double-lumen cannula (Novaport 24 Fr, 270 mm length, 8 mm internal diameter; Novalung, Heilbronn, Germany) was placed into the right common femoral vein (Table 1). This cannula initially provided both outlet and inlet flows through its two lumens, allowing 1 L/min of blood flow through the iLA membrane. This translated into a decreased $PaCO_2$ without any improvement in oxygenation. In this case, the patient's CO was 9.0 L/min (MostCare™ data). Therefore, in order to increase the blood flow through the artificial lung, a second 19 Fr catheter was placed in the left internal jugular vein (OptiSite, Edwards Lifesciences) and used for the inlet flow while the in-site femoral 24 Fr was solely used for outlet flow by connecting both lumens to the circuit with a "Y" piece (3.8") (see Figure 2). With this new configuration, blood flow increased up to 2.0 L/min and a 65.8% gain in PaO_2 was achieved. At this point, CO was 9.5 L/min (Table 1, Figure 1, case 2). Also, in this second case, no device-related complications were observed at any time and the patient died during extracorporeal lung assistance due to septic shock and the development of multi-organ failure after five days.
3. The third case was a 71-year-old man with a severe chronic obstructive pulmonary disease who underwent a robot-assisted esophagectomy. On post-operative day two, the patient developed an acute-on-chronic hypercapnic-hypoxemic pneumonia due to *Pseudomonas aeruginosa* respiratory infection. After an initial ineffective NIPPV treatment, the patient was intubated and the PaO_2/FiO_2 ratio eventually dropped to 56.3; the $PaCO_2$ was 57 mmHg with a pH of 7.37 (Table 1 and Figure 1). A double cannulation was then performed with a 23 Fr venous femoral cannula (Maquet) and a 19 Fr venous right internal jugular vein cannula (Maquet) used as the outlet and inlet, respectively. With a blood flow of 2.0 L/min and a patient CO of 2.5 L/min (MostCare™ data), oxygenation increased by 784.5% (Table 1 and Figure 1). Due to elevated arterial oxygenation, but an inadequate DO_2 of 372 ml/min (Hb 10 g/dL, PaO_2 498 mmHg, SaO_2 100%) caused by low CO, a fluid resuscitation with crystalloids was attempted under pulse contour and transthoracic echocardiographic monitoring: CO increased to 5.5L/min and pump flow reached 2.4 L/min. At this point, arterial blood oxygenation rapidly decreased, reaching a net increase of 13.2% (vs. baseline) while global DO_2 significantly increased to 759 ml/min (Hb 10 g/dl after 1 packed red blood cell transfused, PaO_2 131 mmHg, SaO_2 100%). The patient died 48 hours later due to a worsening of the infection, with shock and multi-organ failure.

The anticoagulation strategy was common in all cases: a bolus of heparin (5000 IU) was administered just after

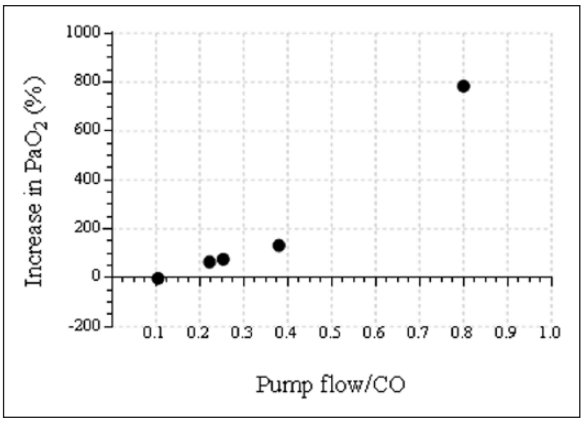

Figure 1. Relationship between pump flow to patient CO ratio and modifications in arterial blood gas.

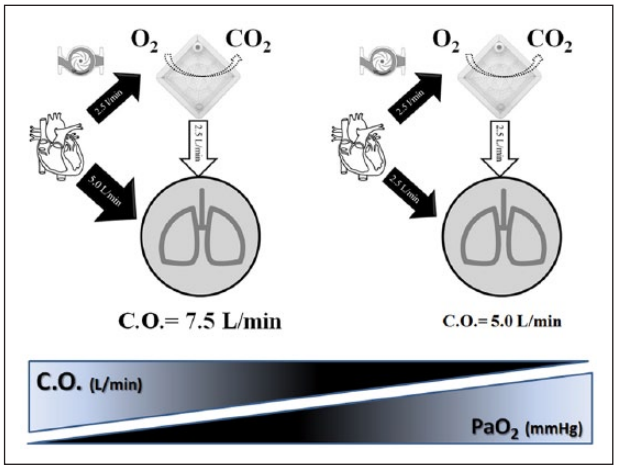

Figure 2. Relationship between pump flow to patient CO and modifications in arterial blood gas. Example A: Patient's CO is 7.5 l/min, resulting in a higher intrapulmonary shunt effect and reduced arterial partial oxygen pressure (PaO_2). Example B: Patient's CO is 5 l/min, resulting in a low intrapulmonary shunt effect (perfusion of poorly ventilated lungs).

the first cannula was placed. The aPTT value was targeted to 50-70 seconds (bedside and laboratory measurements) for the duration of the assistance.

Discussion

In this small case series, extracorporeal support with the iLA-Activve® system effectively improved oxygenation in patients with refractory hypoxemia when a blood flow of at least 2 L/min was attained. According to the manufacturers (www.novalung.com) iLA-Activve® is classified as "Mid Flow – CO_2 removal and partial oxygenation". While studies on CO_2 removal can be found in the literature,[3,4] demonstrations of improved oxygenation are missing. This case series represents the first description, so far, of some interesting contents: 1) CO_2 is cleared effectively, but oxygenation may also improve with a mid-flow device; 2) a system like the iLA-Activve® can be used outside ECMO centers in selected populations of patients; 3) the device can be "tailored" on patient need; 4) the extracorporeal blood flow/CO ratio was found to be a major determinant in the performance of extracorporeal V-V lung assist, with a quasi-linear relationship to the delta PaO_2 increase (Figure 1). That is, in the same patient, an increase in CO or a decrease in blood flow through the artificial membrane translated to a lesser increase in PaO_2 (Figures 1 and 2). The pump flow/CO value may, therefore, help clinicians in their evaluation of V-V extracorporeal support performance.

The efficiency of an extracorporeal respiratory support system depends on a series of important factors.[3] Technical components are clearly of critical importance. These include the artificial lung (membrane), the pump (centrifugal, roller or pumpless arterio-venous systems), the cannulation type (single vs. double), the site (jugular vs. femoral vs. bi-caval) and the size (13-31 Fr).[3] It is commonly considered that the amount of CO_2 removed and O_2 added by the oxygenator is not only dependent on the blood flow through the oxygenator, but also on the gas flow through the oxygenator, as well as the composition of that gas flow (FiO_2). CO_2 clearance is usually efficiently obtained with low extracorporeal blood flows (0.3-0.4 up to 1.0 L/min), using $ECCO_2R$ systems through small catheters[2] thanks to the CO_2 partial pressure gradient across the oxygenator and to its high solubility in water, regardless of the patient's CO. However, when oxygenation is one of the goals, the ratio between the patient's CO and the extracorporeal pump flow becomes a fundamental determinant. In this case, the blood, flowing across the native (diseased) lungs, suffers a "shunt effect" (Figure 2) that decreases arterial oxygenation. Figure 2 summarizes this concept: for a patient with a CO of 5 L/min and an extracorporeal pump flow of 2.5 L/min, 50% of the patient's blood does not cross the artificial lung and does not receive oxygen. In such circumstances, any further CO_2 clearance and/or increase in oxygenation depends both on the capability of the native lung to diffuse gases and on the applied ventilation. In cases where the lungs are substantially non-ventilated (e.g. pneumonia, alveolar infiltrates, ultra-protective ventilation), this 50% of unventilated blood flow (neither circulating into the extracorporeal system nor oxygenated by alveoli) will lead to a significant desaturation due to the intrapulmonary shunt effect. Conversely, a pump flow/CO ratio higher than 60% may be considered sufficient to increase/optimize a patient's oxygenation.[7]

The contribution of CO in predicting the intra-pulmonary shunt effect and its impact on oxygenation has

Table 1. Patients' blood gas analysis, and hemodynamic data and pump information.

Patient	Before lung support					Lung support			4 hours after lung support					
	PaO_2/FiO_2	$PaCO_2$	pH	CO (L/min)	DO_2 (ml/min)	Pump flow L/min (RPM)	O_2 flow (l/min)	Pressures (mmHg)	PaO_2/FiO_2 (%↑)	$PaCO_2$ (%↓)	pH	CO	DO_2 (ml/min)	Pump flow/CO × 100
1 (DC) 20/16 Fr	56.4	44.3	7.34	7.2	810	1.9 (4.400)	4	P1: -5 P2: 77 P3: 71	99.7 (+76.7)	32.3 (-27)	7.41	7.5	905	25.3
2 (SC) 24 Fr	62.6	60.6	7.14	9	1100	1.0 (3.900)	4	P1: -21 P2: 69 P3: 67	61.8 (-1.27)	52.4 (-13.5)	7.23	9.5	1162	10.5
2 (DC) 24/19 Fr	(double cannula configuration)					2.0 (4.500)	6	P1: -15 P2: 109 P3: 101	102 (+65.8)	41 (-21.7)	7.38	9	1175	22.2
3 (DC) -LCOS	56.3	57	7,37	4	361	2.0		P1: -16 P2: 170 P3: 165	498 (+784.5)	28.4 (-50.1)	7.26	2.5	363	80
3 (DC) after volume resuscitation						2.4		P1: -17 P2: 178 P3: 171	131 (+132.6)	26 (-54,4)		5.0	703	48

PaO_2/FiO_2: arterial oxygen partial pressure/inspired oxygen concentration; $PaCO_2$: arterial carbon dioxide partial pressure; CO: cardiac output; DO_2: oxygen delivery; RPM: revolutions per minute; DC: double cannulation; LCOS: Low cardiac output syndrome; P1: before the pump; P2: the membrane; P3: after the membrane.

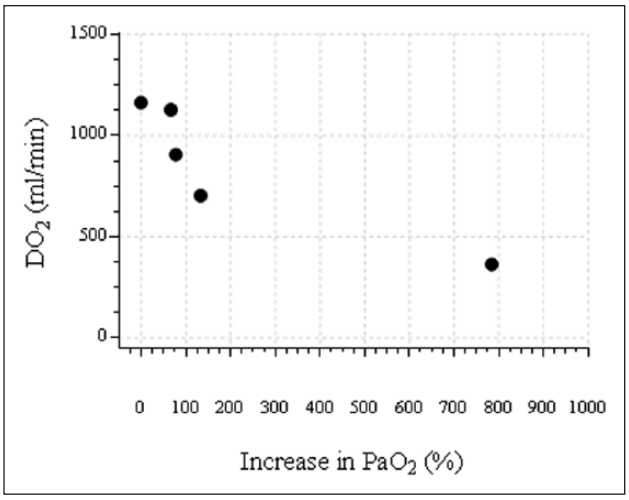

Figure 3. Relationship between increase in PaO_2 and oxygen delivery (DO_2).

been described previously.[8] Interestingly, Guarracino et al. recently described how the relationship between CO and extracorporeal pump flow was optimized by actively decreasing CO in three cases of severe respiratory failure under V-V ECMO.[9] In their study, patients with a CO ≥7 L/min, persistent hypoxemia (O_2= 49, 50 and 54 mmHg, respectively) and an ECMO flow of 5 L/min were treated with esmolol. The beta-blocking agent decreased the heart rate, leading to a reduction of CO from 7.7 to 4.8 L/min. By maintaining the ECMO flow at 5 L/min (pump flow/CO × 100= 104.2), oxygenation improved from 54 to 90 mmHg, from 50 to 94 mmHg and from 49 to 66 mmHg in the three cases, respectively. "Low-flow" ($ECCO_2R$; up to 1.0 L/min) systems and "high-flow" (ECMO; >4.0 L/min) systems have been widely described in literature and their characteristics and performance determinants are well known.[2] However, data on gas exchange for "mid-flow" (1.0-2.5 L/min) systems such as the iLA-Activve® are lacking.

Our cases show that systemic CO is an issue, even with extracorporeal pump flows between 1 and 2.4 L/min. As such, when oxygenation does not increase sufficiently, an increase in pump flow can be attempted. This approach can be very challenging as it requires a more invasive configuration (e.g. from single to double cannulation or from femoral to bi-caval cannulation).[3] Alternatively or contemporarily, a patient's CO can be decreased by using esmolol, as described by Guarracino et al.[9] Clearly, the effects of CO decrease in global DO_2 should be considered before using beta-blockers in critically ill patients. Similarly, when a fluid-responsive V-V ECMO patient receives fluid resuscitation, if the eventual CO improvement causes the pump flow/CO ratio to approach the "critical value" of 50%, an apparently paradoxical decrease in PaO_2 may occur. Hence, in complex clinical conditions, the easy calculation of the extracorporeal pump flow/patient CO ratio can be another useful parameter for interpreting extracorporeal lung assist performance. Clinicians should carefully monitor the hemodynamic conditions of respiratory patients undergoing extracorporeal lung assist and critically evaluate respective flows (systemic and extracorporeal) in order to decide which one of these to manipulate and in what way. In other words, other than trying to reach a specific extracorporeal pump flow/patient CO ratio, it is of critical importance to insure an adequate DO_2 (combination of systemic blood flow, hemoglobin concentration and oxygenation) sufficient to meet the cellular needs at any phase of the disease. The extracorporeal pump flow/patient CO ratio could help the physician in evaluating the performance (CO_2 clearance and/or blood oxygenation) of the applied extracorporeal system in relationship with the systemic blood flow.

In light of this aspect, as shown in patient #3, an initial impressive increase in oxygenation did not change DO_2 at all because of a drop in CO occurring after the vascular cannulation. After CO increase, thanks to fluid volume load, DO_2 increased. Figure 3 shows that higher increases in oxygenation are not necessarily associated with higher DO_2 values. In other words, if the application of an extracorporeal system leads to a significant decrease in CO (impairment of venous return, inflammatory state, etc.), a global worsening of tissue oxygenation may result even if the PaO_2 and arterial oxygen saturation have increased. In these patients, CO estimation is of critical importance and a pulse contour method for CO estimation may represent an interesting solution, with the presence of the extracorporeal circulation being an absolute contraindication for dye dilution methods.

Conclusions

With the iLA-Activve® extracorporeal respiratory support, blood flows over 2.0 L/min across the membrane provided clinically satisfying decarboxylation and improved oxygenation. The ratio between blood flow through the membrane and the patient's CO was a useful indicator for understanding the performance of this extracorporeal system. In the complex and multifactorial evaluation of patients with extracorporeal V-V lung support (e.g. protective ventilation, inspired O_2 concentration, cannulation, pump flow, technical characteristics of the artificial lung), extracorporeal pump flow/patient CO ratio calculations could provide a useful source of additional information.

Declaration of Conflicting Interests

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