This is a peer-reviewed, accepted author manuscript of the following article: De Lazzari, B., Iacovoni, A., Mottaghy, K., Capoccia, M., Badagliacca, R., Vizza, C. D., & De Lazzari, C. (2021). ECMO assistance during mechanical ventilation: effects induced on energetic and haemodynamic variables. *Computer Methods and Programs in Biomedicine*, *202*, [106003]. https://doi.org/10.1016/j.cmpb.2021.106003

ECMO Assistance during Mechanical Ventilation: Effects Induced on Energetic and Haemodynamic Variables.

Beatrice De Lazzari[1]
[1]Department of Engineering, Roma Tre University, Italy
beatrice.delazzari@gmail.com

Attilio Iacovoni[2]
[2] ASST-Papa Giovanni XIII Hospital, Bergamo, Italy
aiacovoni@asst-pg23.it

Khosrow Mottaghy[3]
Institute of Physiology
RWTH Aachen University, Deutsch
kmottaghy@ukaachen.de

Massimo Capoccia[4,5]
[4]Royal Brompton Hospital, Royal Brompton & Harefield NHS Foundation Trust, UK
[5]Department of Biomedical Engineering, University of Strathclyde, Glasgow, UK
capoccia@doctors.org.uk

Roberto Badagliacca[6]
[6]Department of Cardiovascular Respiratory Nephrologic and Geriatric Sciences, Sapienza University of Rome, Italy
roberto.badagliacca@uniroma1.it

Carmine Dario Vizza[6]
[6]Department of Cardiovascular Respiratory Nephrologic and Geriatric Sciences, Sapienza University of Rome, Italy
dario.vizza@gmail.com

Claudio De Lazzari[7,8]
[7]National Research Council, Institute of Clinical Physiology (IFC-CNR), Rome, Italy
Via Palestro, 32 (00185) Rome, Italy
[8]National Institute for Cardiovascular Research (I.N.R.C.), Bologna, Italy
Via Irnerio, 48 (40126) Bologna, Italy
claudio.delazzari@ifc.cnr.it

ABSTRACT

Background and Objective: Simulation in cardiovascular medicine may help clinicians understand the important events occurring during mechanical ventilation and circulatory support. During the COVID-19 pandemic, a significant number of patients have required hospital admission to tertiary referral centres for concomitant mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Nevertheless, the management of ventilated patients on circulatory support can be quite challenging. Therefore, we sought to review the management of these patients based on the analysis of haemodynamic and energetic parameters using numerical simulations generated by a software package named CARDIOSIM©.

Methods: New modules of the systemic circulation and ECMO were implemented in CARDIOSIM© platform. This is a modular software simulator of the cardiovascular system used in research, clinical and e-learning environment. The new structure of the developed modules is based on the concept of lumped (0-D) numerical modelling. Different ECMO configurations have been connected to the cardiovascular network to reproduce Veno-Arterial (VA) and Veno-Venous (VV) ECMO assistance. The advantages and limitations of different ECMO cannulation strategies have been considered. We have used literature data to validate the effects of a combined ventilation and ECMO support strategy.

Results: The results have shown that our simulations reproduced the typical effects induced during mechanical ventilation and ECMO assistance. We focused our attention on ECMO with triple cannulation such as Veno-Ventricular-Arterial (VV-A) and Veno-Atrial-Arterial (VA-A) configurations to improve the hemodynamic and energetic conditions of a virtual patient. Simulations of VV-A and VA-A assistance with and without mechanical ventilation have generated specific effects on cardiac output, coupling of arterial and ventricular elastance for both ventricles, mean pulmonary pressure, external work and pressure volume area.

Conclusion: The new modules of the systemic circulation and ECMO support allowed the study of the effects induced by concomitant mechanical ventilation and circulatory support. Based on our clinical experience during the COVID-19 pandemic, numerical simulations may help clinicians with data analysis and treatment optimisation of patients requiring both mechanical ventilation and circulatory support.

Key words: ECMO; Mechanical ventilation; Pressure volume loop; Lumped parameter model; Software simulation; Clinical environment; Percutaneous left ventricular support; Cannulation

INTRODUCTION

The concept of simulation has become more familiar in medicine with particular reference to patient-specific modelling and training of healthcare professionals [1]. The analysis of the events occurring during concomitant mechanical ventilation and circulatory support has been the subject of significant interest. More specifically, the use of mechanical ventilation in patients on Veno-Arterial extracorporeal membrane oxygenation (VA-ECMO) is aimed at maintaining a protective effect on the lung.

ECMO has become increasingly available for the treatment of a diverse population of critically ill patients and recent reviews have highlighted its indications and the evidence basis to justify its use 2,3. Veno-Arterial extracorporeal membrane oxygenation (VA-ECMO) is considered in the context of cardiac failure 4. Veno-Venous extracorporeal membrane oxygenation is indicated in the context of acute respiratory distress syndrome 5. More recently, ECMO has been considered in the setting of extracorporeal cardiopulmonary resuscitation (ECPR). Despite increased application of the technique, overall survival rates have remained unchanged with a 50-70% range for respiratory support and 40-60% range for cardiac support 6. This apparently disappointing scenario may be partly related to the advanced heart failure status of these patients with increasing associated co-morbidities and partly to unknown areas in need of answers.

In view of the above considerations and based on the experience developed during the COVID-19 pandemic, we developed numerical simulations to reproduce the interactions occurring in ventilated patients on peripheral VA-ECMO support using CARDIOSIM© software 7-11. The initial task consisted of the implementation of a new module based on a 0-D (lumped parameter) numerical model able to reproduce the behavior of the whole systemic circulation. Then, the numerical model of a centrifugal pump was used to simulate ECMO support. During the first phase of the study, the module simulating the management of gas exchanges was not implemented in the platform.

The following ECMO configurations were considered:

- Central Veno-Arterial ECMO (VA_{RA-DA}-ECMO): ECMO takes blood from the right atrium and ejects it into the descending aorta (Fig.1a).
- Veno-Venous ECMO ($VV_{IVC-SVC}$-ECMO): ECMO takes blood from the inferior vena cava and ejects it into the superior vena cava (Fig 1a).
- Veno-Arterial ECMO (VA_{FV-TA}-ECMO): ECMO takes blood from the femoral vein and ejects it into the thoracic aorta (Fig.1b).

The haemodynamic and energetic conditions of patients undergoing circulatory support (VA_{FV-TA}-ECMO) and mechanical ventilation may be improved by activating different functions in the software:

- ✓ Increase the heart inotropism through the administration of drugs that improve myocardial contractility leading to an increase in the ratio between ventricular systolic elastance and arterial elastance (coupling).
- ✓ Insert an intra-aortic balloon pump (IABP) or a temporary left ventricular assist device (Impella FDA approved for this indication).
- ✓ Insert a cannula in the apex of the left ventricle connected to the ECMO inlet. Through this triple cannulation approach, namely Veno-Ventricular-Arterial (VV-A), the ECMO pump draws blood from the left ventricle and the femoral vein and ejects it into the thoracic aorta (Fig. 1b) 12,13.

- ✓ Insert a cannula in the left atrium connected to the ECMO inlet. Through this triple cannulation approach, namely Veno-Atrial-Arterial (VA-A), the ECMO pump draws blood from the left atrium and the femoral vein and ejects it into the thoracic aorta (Fig. 1b) 14,15.

Using the described ECMO configurations, mechanical ventilation (MV) was simulated by changing the mean value of the intrathoracic pressure (between -4 mmHg to +5 mmHg) 16-19.

The following hemodynamic variables were considered: total cardiac output (CO); left ventricular cardiac output, end-diastolic volume (EDV) and end-systolic volume (ESV) for both ventricles, systemic and pulmonary arterial elastance, ventricular-arterial systemic/pulmonary coupling, ventricular ejection fraction for both ventricles, mean pulmonary/systemic arterial pressure, mean left/right atrial pressure. In addition, pulmonary vascular compliance was investigated.

The energetic variables considered for both ventricles were: external work, pressure volume area, potential energy and stroke work.

The aim of this initial study was to focus on the triple ECMO cannulation approach with a view to ascertain its validity and its effectiveness. Another ongoing study will address the combined use of ECMO and IABP or Impella device given its increasing popularity.

MATERIAL AND METHODS

The heart and circulatory numerical network

The cardiovascular network in CARDIOSIM© software consists of seven modules that can assembled in different ways 7-11. The modules are: left and right heart, systemic and pulmonary arterial section, systemic and pulmonary venous section and the coronary circulation. RLC electrical circuits based on 0-D numerical representation are used to model each section of the cardiovascular system 20.

The time-varying elastance concept is used to model the behavior of the left and right native ventricles. Also the left and right atria and the septum are modelled using a time-varying elastance numerical approach 8,9. The electrocardiographic (ECG) signal is synchronized with ventricular, atrial and septal activity 9. The described model allows inter-ventricular and intra-ventricular dyssynchrony to be simulated 9,21.

Different modules of coronary circulation have been implemented in the platform 7,22.

New 0-D numerical model for the systemic circulation

The new module of the systemic circulation (Fig. 2) consists of the following compartments: aortic arch, ascending aorta, descending thoracic and abdominal aorta, renal, hepatic and splanchnic compartments, inferior vena cava and abdominal section, superior vena cava circulation, upper and lower limbs and head sections. Figures 3a and 3b show the electrical analogue of the compartments. Each compartment is modelled with RLC elements based on the lumped (0-D) parameter concept. Pt is the mean intrathoracic pressure. Table 1 shows the systemic circulation variables.

The simulations presented in this paper were performed assembling the new numerical model of the systemic circulation with the pulmonary numerical model represented in

Fig. 3c. The pulmonary circulation consists of main and small pulmonary arterial section, pulmonary arteriole and capillary section and pulmonary venous section 7,23.

New Extracorporeal Membrane Oxygenation (ECMO) numerical model

The ECMO model consists of two devices: a centrifugal pump and an oxygenator. For the purposes of this study, a new numerical module reproducing the behavior of the centrifugal pump 24,25 was implemented in CARDIOSIM© platform. Based on experimental data 24 the following equation describes the pump function:

$$\Delta P = K_A \cdot Q_{PUMP}^2 + \omega \cdot Q_{PUMP} \cdot K_B + \omega^2 \cdot K_C \quad (1)$$

$$Q_{PUMP} = \frac{-\frac{K_B}{K_A} \cdot \omega + \sqrt{\left(\frac{K_B}{K_A}\right)^2 \cdot \omega^2 - \frac{4}{K_A}\left(\omega^2 \cdot K_C - \Delta P\right)}}{2} \quad (2)$$

In Eq. (1) and (2) ΔP is the pressure difference across the pump (head pressure), Q_{PUMP} is the pump flow, ω is the rotational speed of the pump, K_A, K_B and K_C are constants.

Assuming K_A=-1.80E^{-03} [mmHg·sec^2·ml^{-2}], K_B=-1.20E^{-05} [mmHg·sec·ml^{-1}·rpm^{-1}], and K_C=7.3E^{-06} [mmHg·rpm^{-2}], we obtained the curves reported in Fig. 4. The centrifugal pump is connected to the cardiovascular system with two cannulae modelled using RLC elements (Fig. 5). The flow through the inlet cannula is:

$$\begin{aligned} &\left(P_{iCN} - \Delta P\right) = Qi_{CANN} \cdot Ri_{CANN} + \left(\frac{d}{dt} Qi_{CANN}\right) \cdot Li_{CANN} \\ &\left(\frac{d}{dt} \Delta P\right) \cdot Ci_{CANN} = Q_{PUMP} - Qi_{CANN} \end{aligned} \quad (3)$$

P_{iCN} is the pressure at the point of the circulatory network where the inlet cannula is connected. Li_{CANN}, Ri_{CANN} and Ci_{CANN} are the inertance, resistance and compliance of the inlet cannula.

The flow through the outlet cannula is:

$$
\begin{aligned}
&\left(\Delta P - P_{oCN}\right) = Qo_{CANN} \cdot Ro_{CANN} + \left(\frac{d}{dt} Qo_{CANN}\right) \cdot Lo_{CANN} \\
&\left(\frac{d}{dt} \Delta P\right) \cdot Co_{CANN} = Qo_{PUMP} - Qo_{CANN}
\end{aligned}
\tag{4}
$$

P_{oCN} is the pressure at the point of the circulatory network where the outlet cannula is connected. Lo_{CANN}, Ro_{CANN} and Co_{CANN} are the inertance, resistance and compliance of the outlet cannula, respectively.

The ECMO pump can be connected to the cardiovascular network as follows:

- VA_{FV-TA}-ECMO: ECMO receives blood from the femoral vein and ejects it into the thoracic aorta;
- VA_{RA-DA}-ECMO: ECMO receives blood from the right atrium and ejects it into the descending aorta;
- $VV_{IVC-SVC}$-ECMO: ECMO receives blood from the inferior vena cava and ejects it into the superior vena cava.

The following cannulation approach has been implemented in the case of VA_{FV-TA}-ECMO:

- ✓ Veno-Ventricular-Arterial (VV-A) cannulation: a cannula is connected between the left ventricle and the ECMO inlet. Through this triple cannulation approach, the ECMO pump draws blood from the left ventricle and the femoral vein and ejects it into the thoracic aorta;

- ✓Veno-Atrial-Arterial (VA-A) cannulation: a cannula is connected between the left atrium and the ECMO inlet. Through this triple cannulation approach, the ECMO pump draws blood from the left atrium and the femoral vein and ejects it into the thoracic aorta.

Mechanical Ventilation

To simulate the effect induced by mechanical ventilation on the haemodynamic and energetic variables, the mean value of the intrathoracic pressure ranged from Pt=-4 [mmHg] to Pt=+5 [mmHg] 16-19.

Simulation Protocol

Based on pathological conditions reproduced using literature data, ECMO assistance was applied in VA_{FV-TA}-ECMO and VA_{RA-DA}-ECMO mode. The rotational speed of the pump was 4000 rpm for both ECMO configurations and the mean intrathoracic pressure ranged between -4 mmHg and +5 mmHg to simulate MV. The variables measured under these settings were: total cardiac output (CO); left ventricular cardiac output, left and right end-diastolic volume (EDV) and end-systolic volume (ESV), systemic arterial elastance (Ea_{LEFT}), pulmonary arterial elastance (Ea_{RIGHT}), ventricular-arterial systemic/pulmonary coupling, left and right ventricular ejection fraction (EF_{LEFT} and EF_{RIGHT}) mean pulmonary arterial pressure (PAP), mean aortic pressure (AoP), mean left/right atrial pressure (LAP/RAP), pulmonary vascular compliance (PVC), left/right external work (EW_{LEFT}/EW_{RIGHT}), pressure volume area (PVA_{LEFT}/PVA_{RIGHT}) and potential energy (PE_{LEFT}/PE_{RIGHT}) 26-28 and left/right ventricular stroke work (LVSW/RVSW).

We considered three steps to improve left ventricular function during VA_{FV-TA}-ECMO assistance. In the first step, left ventricular contractility was improved by the administration of a drug that increases myocardial contractility. Concomitant mechanical ventilation was maintained and the ratio between ventricular and arterial elastance was evaluated for both ventricles. In the second step, VV-A cannulation was activated during mechanical ventilation. In the last step, VA-A cannulation was considered maintaining ventilation.

RESULTS

Figure 6 shows the effects induced on left/right end diastolic and end systolic ventricular volume (EDV_{LEFT}/EDV_{RIGHT}) by mechanical ventilation when the mean intrathoracic pressure changes from -4 mmHg to +5 mmHg. The level of support for each ECMO configuration was calculated as the relative change respect to baseline conditions. The pump speed was 4000 rpm for all the simulations.

Panel A and B show an increase in EDV_{LEFT} and ESV_{LEFT} during mechanical ventilation and assistance with VA_{FV-TA}-ECMO (VA-ECMO), VA-ECMO and drug administration (VA-ECMO&Drug) and VA_{RA-DA}-ECMO (§VA-ECMO). Panel C and D show a decrease in EDV_{RIGHT} and ESV_{RIGHT} values compared to baseline conditions during VA_{RA-DA}-ECMO assistance. Further reduction in EDV_{RIGHT} and ESV_{RIGHT} is observed when the mean intrathoracic pressure changes from -4 mmHg to +5 mmHg.

Fig. 7 shows the relative changes compared to baseline conditions for the mean left atrial (right) pressure (Panel A and B), aortic pressure (Panel C) and pulmonary pressure (Panel D). VA-A ECMO assistance increases LAP (yellow bars in Panel A), while VA_{RA-DA}-ECMO (§VA-ECMO) assistance decreases mean right atrial and pulmonary pressures. VA-ECMO assistance with drug administration (VA-ECMO&Drug) increases aortic pressure compared to baseline conditions, particularly for positive values of intrathoracic pressure (Panel C). Drug administration does not seem to have significant effects on PAP during VA-ECMO assistance (blue bars in Panel C). Mechanical ventilation produces a sign reversal in the AoP during VA-A ECMO assistance (yellow bars in Panel C). Relative changes in total cardiac output, left ventricular output flow and left (right) ventricular ejection fraction are shown in Fig. 8. The total flow is the sum of the left ventricular output flow and the pump flow during VV-A ECMO, VA-A ECMO and VA_{RA-DA}-ECMO (§VA-ECMO in Fig. 8) assistance. The total flow increases up to 350% (yellow bars in Panel A) compared to baseline CO, while the left ventricular output flow is reduced by 30% (yellow bars in Panel B) regardless of the mean intrathoracic pressure (Pt). Panel C in Fig. 8 shows that only VV-A ECMO assistance increases left ventricular ejection fraction from 40% to 68% when Pt=+5mmHG. The other ECMO configurations decrease EF_{LEFT}, particularly VA_{RA-DA}-ECMO (red bars). Up to 25% reduction in EF_{RIGHT} is also observed during VA_{RA-DA}-ECMO assistance (red bar in Panel D).

Effects induced by different ECMO configurations on left ventricular EW, PVA and PE during MV are shown in Fig. 9. Panel A, B and C show changes during VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO and VV-A ECMO assistance compared to baseline conditions. VV-A ECMO increases EW up to 130% (brown bar) when Pt is +5 mmHg. VA_{FV-TA}-ECMO (VA-ECMO) and VA_{RA-DA}-ECMO reduce EW for each Pt value. Panel D (Fig. 9) shows the normalized LVSW values obtained during baseline conditions, VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO (§VA-ECMO), VA_{FV-TA}-ECMO associated with drug administration (VA-ECMO&Drug), VV-A ECMO and VA-A ECMO assistance with different values of intrathoracic pressure.

Figure 10 shows a screen output produced by CARDIOSIM© software during baseline conditions and different modes of support with potential for real-time analysis in a clinical setting [29]. Left (right) ventricular pressure-volume loops are plotted in window [A] ([B]). VA_{FV-TA}-ECMO and VA_{RA-DA}-ECMO are considered when Pt is -4 mmHg and comparison made with baseline conditions (black loops). The pump rotational speed is 4000 rpm. Blue and red loops represent the left (window [A]) and right (window [B]) pressure-volume loops for VA_{FV-TA}-ECMO and VA_{RA-DA}-ECMO assistance respectively. Panel C shows the LAP (Pla), PAP (Pap), RAP (Pra), SVC (Svc), PVP (Pvp) and IVC (Ivc) mean pressures calculated during the cardiac cycle under VA_{RA-DA}-ECMO assistance. The total flow is 3.9 l/min (Qria=3.9 in Panel C) and the pump flow is 1.37 l/min (Panel F). The values of the energetic variable for the left (right) ventricle are reported in Panel D (E).

Figure 11 shows the effects induced by mechanical ventilation during baseline conditions, VA_{FV-TA}-ECMO (VA-ECMO), VA-A ECMO and VA_{RA-DA}-ECMO (§VA-ECMO) assistance on left and right ventricular loops. Panel A (B) shows the left (right) ventricular loops during baseline and VA_{FV-TA}-ECMO assistance. Blue (green) loops were obtained during baseline conditions and MV with Pt=-4 mmHg (Pt=+5 mmHg), dashed red (white) loops were obtained during VA_{FV-TA}-ECMO assistance and MV with Pt=-4 mmHg (Pt=+5 mmHg). Panel C (D) shows the left (right) ventricular loops during baseline and VA-A ECMO assistance. Blue (green) loops were obtained during baseline conditions and MV with Pt=-4 mmHg (Pt=+5 mmHg), dashed red (white) loops were obtained during VA-A ECMO assistance and MV with Pt=-4 mmHg (Pt=+5 mmHg). Panel E (F) shows the left (right) ventricular loops during baseline and VA_{RA-DA}-ECMO assistance. Blue (green) loops were obtained during baseline conditions and MV with Pt=-4 mmHg (Pt=+5 mmHg), dashed red (white) loops were obtained during VA_{RA-DA}-ECMO assistance and MV with Pt=-4 mmHg (Pt=+5 mmHg). Ventricular loops, the end systolic pressure volume relationship (ESPVR) and the end diastolic pressure volume relationship (EDPVR) allow the evaluation of the trend of EW, PVA and PE during mechanical ventilation under baseline and circulatory assisted conditions.

Effects induced by different ECMO configurations on right ventricular EW, PVA and PE during mechanical ventilation are shown in Fig. 12. Normalized values presented in Panel A, B and C were obtained during baseline conditions, VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO (§VA-ECMO), VA_{FV-TA}-ECMO associated with drug administration (VA-ECMO&Drug), VV-A ECMO and VA-A ECMO assistance with different values of intrathoracic pressure. Right ventricular EW, PVA and PE increased under VA-A ECMO and VV-A ECMO assistance for each Pt value. Positive Pt values reduce EW, PVA and PE. Similar effects on RVSW are observed (Panel D).

Panel A (Fig. 13) shows the relative changes for left (right) Ea_{LEFT}/Ees_{LEFT} (Ees_{RIGHT}/Ea_{RIGHT}) coupling calculated under VA_{FV-TA}-ECMO and VA_{FV-TA}-ECMO with drug administration assistance compared to baseline conditions. Of note, VA_{FV-TA}-ECMO (and drug administration) assistance generates a negative value of $^{*}Ea_{LEFT}/Ees_{LEFT}$ (*Ea/Ees - yellow bars) when Pt is to +5 mmHg. A sign change in Ees_{RIGHT}/Ea_{RIGHT} coupling (Ees/Ea - red bars) occurs when Pt switches from negative to positive values (VA_{FV-TA}-ECMO assistance). Panel B (C) shows the normalized Ea_{LEFT}/Ees_{LEFT} (Ees_{RIGHT}/Ea_{RIGHT}) coupling under baseline conditions, VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO (§VA-ECMO), VA_{FV-TA}-ECMO and drug administration (VA-ECMO&Drug), VV-A ECMO and VA-A ECMO assistance with different values of intrathoracic pressure. Panel D (Fig. 13) shows the relative changes for the pulmonary vascular compliance (PVC) compared to baseline conditions. VA_{RA-DA}-ECMO (§VA-ECMO) reduces PVC compared to baseline conditions for each Pt value.

DISCUSSION

Traditional configurations for ECMO support include the Veno-Venous (VV) through the right internal jugular vein (Avalon cannula) or both femoral veins and the Veno-Arterial (VA) either through the ascending aorta and the right atrium (central cannulation) or through the femoral vessels (peripheral cannulation) 29,31. Hybrid ECMO configurations have been increasingly considered in recent years as an attempt to improve outcome. Triple cannulation such as VV-A or VA-V configurations may help with concomitant cardiac and respiratory failure. Peripheral Veno-Venous-Arterial (VV-A) ECMO consists of double venous cannulation through the right internal jugular vein and the right femoral vein for drainage with right femoral artery cannulation for perfusion. Venous-Arterial-Venous (VA-V) ECMO consists of single venous drainage through the right femoral vein with right femoral artery and right internal jugular vein for perfusion.

An increased left ventricular afterload leading to left ventricular distension may affect the intended beneficial effects of VA-ECMO support. Our simulations show the effect of ECMO support on left and right ventricular function through different configurations. It is evident that full ECMO support has a detrimental effect on ventricular function by increasing afterload and ventricular volume with clear interrelation between the two native ventricles. Figure 6 shows that VV-A ECMO causes almost 100% change in end diastolic volume leading to significant dilatation of the native ventricles. Figure 8 shows that VA-A ECMO has the highest effect on total cardiac output.

Experimental evidence confirms the clinical findings and highlights the presence of reduced left ventricular (LV) ejection fraction and stroke work as markers of LV dysfunction during VA-ECMO support 32. Our simulations show that only VV-A ECMO configuration has a beneficial effect on left ventricular ejection fraction (Fig. 8C).

The impact of VA-ECMO on left ventricular function can be explained in terms of pressure-volume loops and Starling curves as previously suggested 33. Our simulations fit very well in this context. VA-ECMO does not affect LV function directly. When LV afterload is maintained constant at a specific systemic pressure, the Starling curve generated before VA-ECMO support predicts the filling pressure related to any target stroke volume at that systemic pressure. The mechanism by which that specific pressure is achieved does not change the relationship between filling pressure and native LV stroke volume. A maintained Starling relationship during VA-ECMO support may help predict ventricular distension and optimise the balance between LV unloading and systemic perfusion 34. The optimal balance between left ventricular unloading and systemic perfusion remains critical. The degree of LV unloading during VA-ECMO support significantly depends on the absolute flow and the recruitable contractile reserve of the left ventricle. Maintaining a certain degree of left ventricular ejection in the absence of pulmonary edema is highly desirable clinically 34. Optimisation of pump speed, pressure, flow and PEEP (positive end-expiratory pressure) may be required throughout the period of support. After an initial period of stabilization on full ECMO support, partial support may be a more suitable option where the left ventricle continues to eject against a reduced afterload and maintains EDV and ESV within limits reducing the potential for ventricular distension.

Mechanical ventilation induces different effects on EW_{LEFT}, PE_{LEFT} and PVA_{LEFT} under different modes of ECMO assistance (Fig. 9 and Fig. 11). Considering the relative changes compared to baseline conditions, we have observed that mean intrathoracic pressure decreases left ventricular EW_{LEFT} (Fig. 9 panel A) during VA-A ECMO (or VA_{RA-DA}-ECMO) support. The increase in left ventricular PVA_{LEFT} (Fig. 9 panel B) compared to baseline conditions is evident when Pt is +5 mmHg. The described effects on EW_{LEFT} are shown in Fig. 11 (panel C) where the left ventricular loops from baseline and assisted (with VA-A ECMO) conditions are plotted. Panel C shows that EW_{LEFT} decreases for both Pt values during ECMO assistance. In this case PE_{LEFT} decreases during VA-A ECMO support with Pt=-4mmHg (blue and red dashed loops in panels C and E; Fig. 9 panel C) and increases when the mean intrathoracic pressure (green and white dashed loops in panel C and E; Fig. 9 panel C) switches to +5 mmHg. At the same time, right ventricular EW_{RIGHT}, PE_{RIGHT} and PVA_{RIGHT} increase for both Pt values during VA-A ECMO support (Fig. 11, panel B and D) or VA-A ECMO (panel D). VA_{RA-DA}-ECMO assistance induces a reduction in the right heart energetic variables for both values of intrathoracic pressure (Fig. 11, panel F and Fig. 12 panel A, B and C). EW_{LEFT}, PE_{LEFT} and PVA_{LEFT} decrease under VA_{RA-DA}-ECMO support and concomitant mechanical ventilation.

Although a triple cannulation approach may not necessarily give additional benefit, our simulations show some contrasting results between VV-A ECMO and VA-A ECMO configurations. A VV-A ECMO configuration seems to generate significant less left ventricular distension but at the expense of a negative effect on the right ventricle. Besides, both LAP and RAP are also increased but RAP more significantly. Total CO is only slightly increased with significant reduction in LV output flow. Both EF_{LEFT} and

EF_{RIGHT} increase with EF_{LEFT} slightly more significantly. All the energetic parameters (EW, PVA, PE) and LVSW are increased.

A VA-A ECMO configuration seems to generate even less left ventricular distension but still reflects negatively on the right ventricle. LAP is reduced but RAP increases. Also, there is some increase in AoP but even more significantly in PAP. Total CO is increased compared to VV-A ECMO but LV output flow is significantly reduced. EF_{LEFT} is significantly reduced with some increase in EF_{RIGHT}. The energetic parameters are all reduced. In comparison, a VV-A ECMO approach may prove a more effective strategy if required. Nevertheless, partial support would be advisable to enable LV ejection which would balance the potential negative effects, specifically ventricular distension and increased afterload.

A triple cannulation approach is usually considered when a traditional configuration is not achieving the desired outcome. This is quite often an emergency procedure where subsequent measurements are overlooked or not completely recorded limiting data availability for analysis. It is not an easy solvable issue. Nevertheless, our attempts may be just the beginning for further critical analysis despite limited data.

CONCLUSION

ECMO support has become more widely used in recent years and its use is likely to increase. Nevertheless, there are still “grey areas” in need of attention. Our work shows the potential of a simulation approach as an attempt to answer some of the questions. Although this is a preliminary study based on literature data, its outcome has been quite revealing. The next step is aimed at a closer comparison with “real life” scenarios with a view to treatment optimisation and outcome prediction. The use of IABP and Impella device will be considered too.

Table1 Systemic circulation variables

AoP	Aortic blood pressure [mmHg]
AAP	Ascending aorta&Aortic arch pressure [mmHg]
R_{AA1}	Ascending aorta&Aortic arch I resistance [$mmHg \cdot cm^{-3} \cdot sec$]
L_{AA1}	Ascending aorta&Aortic arch I inertance [$mmHg \cdot cm^{-3} \cdot sec^{2}$]
C_{AA1}	Ascending aorta&Aortic arch I compliance [$mmHg^{-1} \cdot cm^{-3}$]
DAP	Descending aorta&Aortic arch pressure [mmHg]
R_{AA2}	Descending aorta&Aortic arch I resistance [$mmHg \cdot cm^{-3} \cdot sec$]
L_{AA2}	Descending aorta&Aortic arch I inertance [$mmHg \cdot cm^{-3} \cdot sec^{2}$]
C_{AA2}	Descending aorta&Aortic arch I compliance [$mmHg^{-1} \cdot cm^{-3}$]
SVCP	Superior vena cava pressure [mmHg]
R_{supVC}	Superior vena cava resistance [$mmHg \cdot cm^{-3} \cdot sec$]
C_{supVC}	Superior vena cava compliance [$mmHg^{-1} \cdot cm^{-3}$]
THP	Aortic thoracic pressure [mmHg]
R_{AT1}	Aortic thoracic resistance [$mmHg \cdot cm^{-3} \cdot sec$]
L_{AT1}	Aortic thoracic inertance [$mmHg \cdot cm^{-3} \cdot sec^{2}$]
C_{AT1}	Aortic thoracic compliance [$mmHg^{-1} \cdot cm^{-3}$]
ABD_{I}	Abdominal pressure (Tract I) [mmHg]
R_{ABI}	Abdominal resistance (Tract I) [$mmHg \cdot cm^{-3} \cdot sec$]
L_{ABI}	Abdominal inertance (Tract I) [$mmHg \cdot cm^{-3} \cdot sec^{2}$]
C_{ABI}	Abdominal compliance (Tract I) [$mmHg^{-1} \cdot cm^{-3}$]
ABD_{II}	Abdominal pressure (Tract II) [mmHg]
R_{ABII}	Abdominal resistance (Tract II) [$mmHg \cdot cm^{-3} \cdot sec$]
L_{ABII}	Abdominal inertance (Tract II) [$mmHg \cdot cm^{-3} \cdot sec^{2}$]
C_{ABII}	Abdominal compliance (Tract II) [$mmHg^{-1} \cdot cm^{-3}$]
SP	Splanchnic pressure [mmHg]
R_{SP1}	Variable splanchnic resistance [$mmHg \cdot cm^{-3} \cdot sec$]
R_{SP2}	Splanchnic resistance [$mmHg \cdot cm^{-3} \cdot sec^{2}$]
C_{SP}	Splanchnic compliance [$mmHg^{-1} \cdot cm^{-3}$]
LEP	Legs pressure [mmHg]
R_{LE1}	Variable legs resistance [$mmHg \cdot cm^{-3} \cdot sec$]
R_{LE2}	Legs resistance [$mmHg \cdot cm^{-3} \cdot sec$]
C_{LE}	Legs compliance [$mmHg^{-1} \cdot cm^{-3}$]
HDP	Head pressure [mmHg]
R_{HD1}	Variable head resistance [$mmHg \cdot cm^{-3} \cdot sec$]
R_{HD2}	Head resistance [$mmHg \cdot cm^{-3} \cdot sec$]
C_{HD}	Head compliance [$mmHg^{-1} \cdot cm^{-3}$]
ARP	Arms pressure [mmHg]
R_{ARM1}	Variable arms resistance [$mmHg \cdot cm^{-3} \cdot sec$]
R_{ARM2}	Arms resistance [$mmHg \cdot cm^{-3} \cdot sec$]
C_{ARM}	Arms compliance [$mmHg^{-1} \cdot cm^{-3}$]
HP	Hepatic pressure [mmHg]
R_{HEP1}	Variable hepatic resistance [$mmHg \cdot cm^{-3} \cdot sec$]
R_{HEP2}	Hepatic resistance [$mmHg \cdot cm^{-3} \cdot sec$]
C_{HEP}	Hepatic compliance [$mmHg^{-1} \cdot cm^{-3}$]

KP	Renal pressure [mmHg]
R_{KID1}	Variable renal resistance [mmHg·cm^{-3}·sec]
R_{KID2}	Renal resistance [mmHg·cm^{-3}·sec]
C_{KID}	Renal compliance [mmHg^{-1}·cm^{-3}]
P_B	Variable abdominal pressure [mmHg]
ABP_{INVC}	Abdominal inferior vena cava pressure [mmHg]
R_{AbdVC}	Abdominal inferior vena cava resistance [mmHg·cm^{-3}·sec]
C_{AbdVC}	Abdominal inferior vena cava compliance [mmHg^{-1}·cm^{-3}]
C_{InfVC}	Inferior vena cava compliance [mmHg^{-1}·cm^{-3}]
R_{InfVC1}	First inferior vena cava resistance [mmHg·cm^{-3}·sec]
R_{InfVC2}	Second inferior vena cava resistance [mmHg·cm^{-3}·sec]
R_{THOR}	Thoracic resistance [mmHg·cm^{-3}·sec]

ABBREVIATIONS

ECMO	Extracorporeal Membrane Oxygenation
VA ECMO	Veno-Arterial ECMO
VV ECMO	Veno-Venous ECMO
MV	Mechanical Ventilation
VV-A ECMO	Veno-Ventricular-Arterial ECMO
VA-A ECMO	Veno-Atrial-Arterial ECMO
$VA_{RA\text{-}DA}$-*ECMO*	Central VA-ECMO, the centrifugal pump takes blood from the right atrium and ejects it into descending aorta
$VV_{IVC\text{-}SVC}$-*ECMO*	VV-ECMO, the centrifugal pump takes blood from the inferior vena cava and ejects it into superior vena cava
$VA_{FV\text{-}TA}$-*ECMO*	VA-ECMO, the pump takes blood from the femoral vein and ejects it into thoracic aorta
VVA-ECMO	Peripheral Veno-Venous-Arterial ECMO consists of double venous cannulation through the right internal jugular vein and the right femoral vein for drainage with right femoral artery cannulation for perfusion.
VAV-ECMO	Venous-Arterial-Venous ECMO consists of single venous drainage through the right femoral vein with right femoral artery and right internal jugular vein for perfusion.
IABP	Intraaortic Balloon Pump
FDA	U.S. Food and Drug Administration
CO	Cardiac output [L/min]
PAP	Mean Pulmonary Arterial Pressure [mmHg]
LAP (RAP)	Mean Left(Right) Atrial Pressure [mmHg]
ECG	Electrocardiographic
AoP	Mean aortic blood pressure [mmHg]
Ea_{LEFT}	Systemic arterial elastance [mmHg/ml]
Ea_{RIGHT}	Pulmonary arterial elastance [mmHg/ml]
EW_{LEFT} (EW_{RIGHT})	Left (Right) ventricular external work
PVA_{LEFT} (PVA_{RIGHT})	Left (Right) ventricular pressure-volume area
PE_{LEFT} (PE_{RIGHT})	Left (Right) ventricular potential energy
EDV	End-diastolic volume [ml]
ESV	End-systolic volume [ml]
SV	Stroke volume [ml]
HR	Heart rate [bpm]
EF_{LEFT} (EF_{RIGHT})	Left (Right) ventricular ejection fraction
LVSW (RVSW)	Left (Right) Ventricular Stroke Work
TOTAL CO	Total Cardiac Output=Left Ventricular Output Flow+ Pump Flow
LV	Left Ventricular
ESPVR (EDPVR)	End Systolic (Diastolic) Pressure Volume Relationship
PEEP	Positive End-Expiratory Pressure

De Lazzari Claudio

FUNDING AND CONFLICT OF INTEREST

None

ACKNOWLEDGEMENTS

None

REFERENCES

1. F. Lateef, Simulation-based learning: Just like the real thing, J. Emerg. Trauma Shock. 3(4) (2010) 348–352. DOI 10.4103/0974-2700.70743.

2. J.J Squiers, B. Lima, J.M. DiMaio. Contemporary extracorporeal membrane oxygenation therapy in adults: Fundamental principles and systematic review of the evidence, J. Thorac. Cardiovasc. Surg. 152 (2016) 20-32.

3. G.W.Y. Ng, H.J. Yuen, K.C. Sin, A.K.H. Leung, Y.K.W. Au, K.Y. Lai, Clinical use of venoarterial extracorporeal membrane oxygenation, Hong Kong Med. J. 23 (2017) 282-290.

4. M.O. Maybauer, A. Vohra, N.J. O'Keeffe et al. Extracorporeal membrane oxygenation in adult congenital heart disease: a case series and literature review, Crit. Care Resusc. 19 (Suppl. 1) (2017) 15-20.

5. L. Szentgyorgyi, C. Shepherd, K.W. Dunn, P. Fawcett, J.M. Barker, P. Exton, M.O. Maybauer, Extracorporeal membrane oxygenation in severe respiratory failure resulting from burns and smoke inhalation injury, Burns 44(5) (2018) 1091-1099.

6. J.B. Clark, S. Wang, D.A. Palanzo, R. Wise, L.D. Baer, C. Brehm, A. Ündar, Current techniques and outcomes in extracorporeal life support, Artif. Organs 39(11) (2015) 926–930.

7. C. De Lazzari, D. Stalteri. 2011-2019, CARDIOSIM© Website. Original website platform regarding the implementation of the cardiovascular software simulator CARDIOSIM©. (https://cardiosim.dsb.cnr.it/).

8. C. De Lazzari, et al., Interactive simulator for e-Learning environments: a teaching software for health care professionals, Biomed Eng Online. 13 (2014) 172.

9. C. De Lazzari, Interaction between the septum and the left (right) ventricular free wall in order to evaluate the effects on coronary blood flow: numerical simulation, Comput. Methods. Biomech. Biomed. Eng. 15(12) (2012) 1359-1368.

10. M. Capoccia, S. Marconi, S.A. Singh, et al., Simulation as a preoperative planning approach in advanced heart failure patients. A retrospective clinical analysis, Biomed Eng Online. 17(1) (2018) 52.

11. M. Capoccia, S. Marconi, and C. De Lazzari, Decision-making in advanced heart failure patients requiring LVAD insertion: Can preoperative simulation become the way forward? A case study, J. Biomed. Eng. Inform. 4(2) (2018) 8-20.

12. E. Pavlushkov, M. Berman, K. Valchanov, Cannulation techniques for extracorporeal life support, Ann. Transl. Med. 5(4) (2017) 70. DOI 10.21037/atm.2016.11.47.

13. S. Fukushima, N. Tadokoro, A. Koga, et al. Central conversion from peripheral extracorporeal life support for patients with refractory congestive heart failure, J. Artif. Organs 23 (2020) 214–224. DOI 10.1007/s10047-020-01157-0.

14. B. Kar, L.E. Adkins, A.B. Civitello, P. Loyalka, N. Palanichamy, C.J. Gemmato, T.J. Myers, et al., Clinical Experience with the TandemHeart® Percutaneous Ventricular Assist Device, Tex .Heart. Inst. J. 33(2) 2006 111–115.

15. H. Satoh, T. Kobayashi, S. Nakano, Y. Shimazaki, M. Kaneko, et al., Clinical Experience with Percutaneous Left Ventricular Support Using Transseptal Left Atrial - Femoral Artery Bypass, In: T. Akutsu, H. Koyanagi (Eds) Heart Replacement. Springer, Tokyo. DOI 10.1007/978-4-431-67023-0_27.

16. C. De Lazzari, M. Darowski, G. Ferrari, F. Clemente, The influence of left ventricle assist device and ventilatory support on energy-related cardiovascular variables, Med. Eng. Phys. 20(2) (1998) 83-91.

17. C. De Lazzari, B. Quatember, F. Fedele et al., Mechanical ventilation and thoracic artificial lung assistance during mechanical circulatory support with PUCA pump: In silico study, Comput Methods Programs Biomed, 113 (2) 2014 642-654.

18. C. De Lazzari, M. Darowski, G. Ferrari, et al., The impact of rotary blood pump in conjunction with mechanical ventilation on ventricular energetic parameters: Numerical Simulation, Methods Inf. Med. 45 (5) 2006 574-583.

19. C. De Lazzari, M. Darowski, G. Ferrari, et al., Energetic parameter changes with mechanical ventilation in conjunction with BVAD assistance, J. Med. Eng. Technol. 26 (2) 2002 63-70.

20. S. Marconi, M. Capoccia and C. De Lazzari, Mathematical Modelling of the Cardiovascular System, In: M. Capoccia and C. De Lazzari (Eds) Concepts, Mathematical Modelling and Applications in Hart Failure. Nova Science Publisher, New York, 2019 119-158.

21. C. De Lazzari, S. Marconi and M. Capoccia, Physiology of Ventricular Interdependence, In: M. Capoccia and C. De Lazzari (Eds) Concepts, Mathematical Modelling and Applications in Hart Failure. Nova Science Publisher, New York, 2019 77-118.

22. C. De Lazzari, A. L'Abbate, M. Micalizzi, M.G. Trivella, D. Neglia, Effects of amlodipine and adenosine on coronary haemodynamics: in vivo study and

numerical simulation, Comput. Methods Biomech. Biomed. Eng. 17 (15) 2014 1642-52.

23. C. De Lazzari, B. Quatember, Cardiac Energetics in Presence of Lung Assist Devices: In Silico Study, Model. Num. Simul. Mater. Sci. 6(3) 2016 41-57.

24. B. Kevin, B.G. David, M.L Howard, R.J. Scott, et al., HeartMate III: pump design for a centrifugal LVAD with a magnetically levitated rotor, Am. Soc. Artif. Intern. Organs J. 47 2001 401–405.

25. Y. Shi, T. Korakianitis, Impeller-pump model derived from conservation laws applied to the simulation of the cardiovascular system coupled to heart-assist pumps, Comput. Biol. Med. 93 2018 127-138.

26. H. Suga, K. Sagawa, A.A. Shoukas, Load Independence of the Instantaneous Pressure-Volume Ratio of the Canine Left Ventricle and Effects of Epinephrine and Heart Rate on the Ratio, Circ. Res. 32 (1973) 314-322.

27. K. Sagawa, L. Maughan, H. Suga, K. Sunagawa, Cardiac contraction and the Pressure-Volume relationships. Oxford University Press, New York, 1988.

28. W.L. Maughan, K. Sunagawa, and K. Sagawa, Ventricular systolic interdependence: volume elastance model in isolated canine hearts, Am. J. Physiol. Heart Circ. Physiol. 253 (1987) H1381-H1390.

29. M. Broomé, D.W. Donker. Individualized real-time clinical decision support to monitor cardiac loading during venoarterial ECMO, J. Transl. Med. 14(4) (2016). DOI 10.1186/s12967-015-0760-1

30. A. Brasseur, S. Scolletta, R. Lorusso, F.S. Taccone, Hybrid extracorporeal membrane oxygenation, J. Thorac. Dis. 10(Suppl. 5) (2018) S707-S715.

31. E. Pavlushkov, M. Berman, K. Valchanov, Cannulation techniques for extracorporeal life support, Ann. Transl. Med. 5(4) (2017) 70.

32. P. Schiller, P. Vikholm, L. Hellgren, Experimental Venoarterial Extracorporeal Membrane Oxygenation Induces Left Ventricular Dysfunction, ASAIO J. 62 (2016) 518-524.

33. M.L. Dickstein, The Starling Relationship and Veno-Arterial ECMO: Ventricular Distension Explained, ASAIO J. 64 (2018) 497-501.

34. D.W. Donker, D. Brodie, J.P.S. Henriques, M. Broomé, Left Ventricular Unloading During Veno-Arterial ECMO: A Simulation Study. ASAIO J. 65 (2019) 11-20.

Figure Captions List

Fig. 1a Schematic representation of VA_{RA-DA}-ECMO and $VV_{IVC-SVC}$-ECMO configurations. In VA_{RA-DA}-ECMO mode, the centrifugal pump takes blood from the right atrium (continuous blue line) and ejects it into descending aorta (continuous red line). In $VV_{IVC-SVC}$-ECMO mode, the centrifugal pump takes blood from the inferior vena cava (dashed blue line) and ejects it into superior vena cava (dashed red line).

Fig. 1b Schematic representation of VA_{FV-TA}-ECMO configuration. The centrifugal pump takes blood from the femoral vein (continuous blue line) and ejects it into thoracic aorta (TA) (continuous red line). In the triple cannulation VV-A ECMO, the pump takes blood from FA (continuous blue line) and LV (dashed lilac line), respectively and ejects it into TA (continuous red line). In the triple cannulation VA-A ECMO, the pump takes blood from FA (continuous blue line) and LA (dashed blue line), respectively and ejects it into TA (continuous red line).

Fig. 2 Schematic representation of the compartments of the new numerical model of the systemic circulation. The compartments are: ascending and descending aorta with aortic arch, thoracic (with thoracic resistance R_{THOR}), upper limbs and head, superior and inferior vena cava, renal and hepatic, splanchnic, abdominal and lower limbs. Atrial and ventricular septa are interdependent and they are modelled using time-varying elastance model. Mitral, tricuspid, pulmonary and aortic valves are modelled using resistance and diode. A model with inverse resistance is used to simulate pulmonary and tricuspid regurgitation.

Fig. 3a Electrical analogue of ascending and descending aorta with aortic arch, superior vena cava, thoracic and the first tract of the abdominal aorta. R_{THOR} represents the large thoracic resistance. The reported RLC elements are explained in Table 1.

Fig. 3b Electrical analogue of upper and lower limbs and head. The reported RLC elements are explained in Table 1.

Fig. 3c Electrical analogue of the second tract of the abdominal aorta, inferior vena cava, renal, hepatic and splanchnic compartments. The reported RLC elements are explained in Table 1

Fig. 4 Centrifugal pump waveforms reproduced for different rotational speed using Eq.1. ΔP is the head pump pressure.

Fig. 5 Electric analogue of the inlet and outlet cannula connected to the centrifugal pump. Qo_{CANN} (Qi_{CANN}) is the flow through the output (input) cannula. Ro_{CANN}, Co_{CANN} and Lo_{CANN} (Ri_{CANN}, Ci_{CANN} and Li_{CANN}) are the resistance, compliance and inertance of the outlet (inlet) cannula.

Fig.6 Relative changes calculated in comparison to baseline conditions for different ECMO configurations and concomitant mechanical ventilation. Panel A (B) shows the relative changes for the left ventricular end-diastolic (end-systolic) volume calculated in comparison to baseline conditions for VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO (§VA-ECMO), VA-ECMO and drug administration (VA-ECMO&Drug), Veno-Atrial-Arterial ECMO (VA-A ECMO) and Veno-Ventricular-Arterial

ECMO (VV-A ECMO) assistance. The mean intrathoracic pressure (Pt) ranged between -4 to +5 mmHg to simulate the effects induced by mechanical ventilation. Panel C (D) shows the relative changes for the right ventricular end-diastolic (end-systolic) volume.

Fig. 7 Relative changes calculated in comparison to baseline conditions for different ECMO configurations with concomitant MV. Panel A (B) shows the relative changes for the mean left (right) atrial pressure.

VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO (§VA-ECMO), VA-ECMO and drug administration (VA-ECMO&Drug), Veno-Atrial-Arterial ECMO (VA-A ECMO) and Veno-Ventricular-Arterial ECMO (VV-A ECMO) are the different mode of assistance. Panel C (D) shows the relative changes for the mean aortic pressure (AoP) and the mean pulmonary pressure (PAP).

Fig. 8 Relative changes calculated in comparison to baseline conditions for different ECMO configurations with concomitant MV. Panel A shows the relative changes for the total cardiac output. Total CO represents the sum of the centrifugal pump flow and the left ventricular output flow (Panel B). Panel C (D) shows the relative changes of left (right) ventricular ejection fraction.

The simulations included the following configurations: VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO (§VA-ECMO), VA-ECMO and drug administration (VA-ECMO&Drug), Veno-Atrial-Arterial ECMO (VA-A ECMO) and Veno-Ventricular-Arterial ECMO (VV-A ECMO). The pump rotational speed was 4000 rpm.

Fig. 9 Panel A, B and C show the relative changes calculated in comparison to baseline conditions for different ECMO configurations and concomitant mechanical ventilation. The simulations included VA_{RA-DA}-ECMO (§VA-ECMO), Veno-Atrial-Arterial ECMO (VA-A ECMO) and Veno-Ventricular-Arterial ECMO (VV-A ECMO). The pump rotational speed was 4000 rpm.

Panel A shows the relative changes for the left ventricular external work (EW_{LEFT}). Panel B and C show the relative changes for the left ventricular pressure volume area (PVA_{LEFT}) and potential energy (PE_{LEFT}), respectively.

Panel D shows the normalized left ventricular stroke work (LVSW) values obtained when baseline conditions, VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO (§VA-ECMO), VA_{FV-TA}-ECMO associated with drug administration (VA-ECMO&Drug), VV-AECMO and VA-A ECMO assistance were simulated with different values of intrathoracic pressure.

Fig. 10 Screen output generated by CARDIOSIM© platform. Left (right) ventricular pressure-volume loops corresponding to different circulatory conditions are plotted in window A (B). The black ventricular loops were obtained simulating the baseline conditions as described in the text. The red ventricular loops were generated during VA_{FV-TA}-ECMO support in comparison to baseline conditions. The blue ventricular loops were obtained during VA_{RA-DA}-ECMO assistance was applied. The mean intrathoracic pressure (Pt) was -4 mmHg for all the simulations. Panel C shows the mean values (calculated during the cardiac cycle). Panel C shows the heart rate (HR) the systolic, diastolic and mean aortic pressures, the mean pressures in different tracts of circulatory network, the input and output flow for each atrium and ventricle (Qlia/Qria is the mean input flow in the left/right atrium; Qlo/Qro is the mean left/right ventricular output flow; Qli/Qri is the mean left/right ventricular input flow). The stroke volume (SV), the end systolic/diastolic volume (Ves/Ved) and the ejection fraction for both ventricles are presented in Panel C. Finally, systolic and diastolic pulmonary pressures are also presented. Paned D (E) shows the mean values of left (right) ventricular energetic variables. The mean value of the pump flow is reported in Panel F. All the values were calculated during VA_{RA-DA}-ECMO assistance.

Fig. 11 Panel A (B) shows the left (right) ventricular loops during baseline and VA_{FV-TA}-ECMO assistance. Blue (green) loops were obtained during baseline conditions and MV with Pt = -4 mmHg (Pt = +5 mmHg), dashed red (white) loops were obtained during VA_{FV-TA}-ECMO assistance and MV with Pt = -4 mmHg (Pt = +5 mmHg). Panel C (D) shows the left (right) ventricular loops during baseline and VA-A ECMO assistance. Blue (green) loops were obtained during baseline conditions and MV with Pt = -4 mmHg (Pt = +5 mmHg), dashed red (white) loops were obtained during VA-A ECMO assistance and MV with Pt = -4 mmHg (Pt = +5 mmHg). Panel E (F) shows the left (right) ventricular loops during baseline and VA_{RA-DA}-ECMO assistance. Blue (green) loops were obtained during baseline conditions and MV with Pt = -4 mmHg (Pt = +5 mmHg), dashed red (white) loops were obtained during VA_{RA-DA}-ECMO assistance and MV with Pt = -4 mmHg (Pt = +5 mmHg). All the data were stored in Excel files and subsequently processed.

Fig. 12 Normalized values of external work, pressure volume area, potential energy calculated for the right ventricle are shown in Panel A, B and C, respectively.

Panel D shows the normalized values calculated for the right ventricular stroke work (RVEW). The normalized values were obtained when baseline conditions, VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO (§VA-ECMO), VA_{FV-TA}-ECMO associated with drug administration (VA-ECMO&Drug), VV-A ECMO and VA-A ECMO assistance were simulated with different values of intrathoracic pressure.

Fig. 13 Panel A shows the effects induced on left and right ventricular arterial coupling during VA_{FV-TA}-ECMO (VA-ECMO) and VA_{FV-TA}-ECMO associated with drug administration were simulated starting from basal conditions. The relative changes were calculated in comparison to baseline conditions. Ea/Ees and Ees/Ea (*Ea/Ees and *Ees/Ea) represent the left and right coupling calculated during VA_{FV-TA}-ECMO (VA_{FV-TA}-ECMO associated with drug administration) assistance was applied, respectively. Panel B (C) shows the normalized values of the left (right) coupling Ea_{LEFT}/Ees_{LEFT} (Ea_{RIGHT}/Ees_{RIGHT}) obtained when baseline conditions, VA_{FV-TA}-ECMO (VA-ECMO), VA_{RA-DA}-ECMO (§VA-ECMO), VA_{FV-TA}-ECMO associated with drug administration (VA-ECMO&Drug), VV-A ECMO and VA-A ECMO assistance were simulated with different values of intrathoracic pressure. Panel D shows the relative changes calculated for the pulmonary vascular compliance (PVC).