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Ashleigh Xie, Tristan D. Yan MD, MS, PhD, FRACS, Paul Forrest MBChB, FANZCA

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Recirculation in Veno-venous Extracorporeal Membrane Oxygenation

Authors: Ashleigh Xie¹; Tristan D. Yan¹-³, MD, MS, PhD, FRACS; Paul Forrest³-⁴, MBChB, FANZCA

Corresponding Author:
Email: z3372411@unsw.edu.au
Address: Suite 304, 100 Carillon Avenue, Newtown, NSW, 2042, Australia

Institutions: ¹The Collaborative Research (CORE) Group, Macquarie University, Sydney, Australia; ²Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital; ³University of Sydney; ⁴Department of Cardiothoracic Anesthesia and Perfusion, Royal Prince Alfred Hospital, Sydney, Australia

Abstract:
Despite the increasing use of veno-venous extracorporeal membrane oxygenation (VV-ECMO) to treat severe respiratory failure, recirculation remains a common complication that may result in severe hypoxemia and end-organ damage. The present review therefore examines updated evidence for the causes, measurement, and management of recirculation. Six electronic databases were searched from their dates of inception to January 2016, and 38 relevant studies were selected for analysis. This review revealed that currently, recirculation is typically calculated from measurement of blood oxygen saturations, although limited evidence suggests that oxygen content may provide a more accurate measure. Dilutional ultrasound may play an additional role in dynamic quantitative monitoring of recirculation, but further human studies are required to validate its clinical use. Although cannula configuration appears to be a key contributor to recirculation in addition to factors such as ECMO flow rate, there are insufficient comparative clinical studies to recommend an optimal cannulation technique for minimizing recirculation. Existing evidence suggests that the dual-lumen cannula may have a low recirculation fraction, but only if correctly positioned. This review underscores the need for more robust clinical and laboratory studies to effectively evaluate and address the persistent problem of recirculation.

Keywords
extracorporeal membrane oxygenation; extracorporeal circulation; recirculation
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Introduction
In recent years, there has been renewed interest in the use of veno-venous extracorporeal membrane oxygenation (VV-ECMO) for severe acute respiratory distress syndrome (ARDS), because it facilitates protective lung ventilation and has been shown to improve survival (1, 2). Furthermore, VV-ECMO is associated with fewer vascular complications compared to other extracorporeal pulmonary support devices that require arterial cannulation, such as the Pumpless Interventional Lung Assist (PILA) and veno-arterial ECMO (VA-ECMO) (3, 4).

However, unlike these devices, VV-ECMO can be complicated by recirculation. This occurs when a fraction of oxygenated blood delivered by the infusing cannula is withdrawn by the draining cannula before entering the systemic circulation. High recirculation volumes markedly decrease the efficacy of VV-ECMO and may contribute to severe hypoxemia and end-organ damage. It is therefore essential that this complication is recognized and managed. The present review examines the causes, measurement and management of recirculation.

Material and Methods
A literature review was performed by searching six electronic databases, including MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effects (DARE), from their dates of inception to January 2016. To maximize the sensitivity of the search, the following terms were combined: (extracorporeal membrane oxygenation OR extracorporeal circulation OR ECMO) AND (recirculation), as either keywords or MeSH terms. The reference lists of articles obtained were also reviewed in order to identify additional relevant studies.

Both in-vitro and in-vivo studies, including mock loop, animal and human trials, were included in the review. When institutions published duplicate studies with overlapping sample populations, only the most recent articles were reviewed. Case reports and conference abstracts were also analyzed. Only studies published in the English language were selected.

Mechanism of Recirculation
Recirculation occurs when oxygenated blood infused by the return cannula is withdrawn by the access cannula before it reaches the systemic circulation. This may result in insufficient oxygen delivery with subsequent hypoxemia, and is one of the main factors that limit the efficacy of VV-ECMO (5, 6).

Because the distance between the infusing and draining cannula tips is one of the main determinants of recirculation, ECMO cannula configuration has been the focus of most studies on recirculation (5). However, few studies have quantitatively compared recirculation amongst common used VV-ECMO cannulation configurations, including femoro-femoral and femoro-jugular techniques. Mock circulation loop studies by Xie et al. (2015) and Jayewardene et
al. (2015) demonstrated higher recirculation fractions for femoro-femoral and femoro-jugular configurations compared to dual-lumen cannulation, based on oxygen content calculations in crystalloid solution (7, 8). Current blood-based mock loop studies, meanwhile, have not yielded consistent results (8).

Other contributors to recirculation include patient movement (such as rotation of the head and neck), which may affect cannula position; volume status; cardiac output; and ECMO flow rate (9-13). Higher ECMO flow rate, in particular, has been shown in multiple studies to increase recirculation fractions. Sreenan et al. (2000) and Van Heijst et al. (2001) both demonstrated that increased recirculation occurred at higher VV-ECMO pump flows, using a dual-lumen cannula in animal models and measuring recirculation based on thermodilution and oxygen saturation calculations respectively (11, 13). Broman et al. (2015), using a mock circulation loop, similarly showed a positive correlation between recirculation (based on oxygen saturation measurements) and ECMO flow rate up to 5L/min with various cannula placements in the right atrium and vena cavae (10). Togo et al. (2015) demonstrated similar findings in goats, cannulated in various configurations (including the right atrium and/or vena cavae) (12). However, they also found that oxygen saturation and partial pressure (PaO₂) increased at higher ECMO flow rates, indicating that oxygen delivery increased in spite of increased recirculation (12).

Nonetheless, it should be noted that these studies all had limitations, including small sample sizes, animal-based or in-vitro design, and considerable variation in methodology for quantifying recirculation.

Quantification of Recirculation
A range of techniques has been developed in the attempt to accurately measure recirculation.

Formulae for Recirculation
Recirculation is calculated as a proportion of the volume of oxygenated blood infused by the ECMO circuit that is then immediately withdrawn into the draining ECMO cannula, as expressed by Equation 1.

\[
\text{Recirculation} \, (\%) = \frac{\text{Oxygenated blood drained from infusing cannula}}{\text{Net blood drained}} \times 100\%
\]

Formula 1: Simplified recirculation equation. Blood drained is expressed in litres per minute.

Applying the law of conservation of mass of oxygen gives rise to the following formula:

\[
\text{Recirculation} \, (\%) = \frac{ctO_2 \, Draining - ctO_2 \, Mixed \, ven}{ctO_2 \, Infusing - ctO_2 \, Mixed \, ven} \times 100\%
\]

Formula 2: Recirculation formula based on oxygen content. \(ctO_2 \, Draining\), oxygen content (g/dL) in draining cannula; \(ctO_2 \, Infusing\), oxygen content (g/dL) in infusing
cannula; \( ctO_2^{\text{Mixed ven}} \), oxygen content (g/dL) of mixed venous blood prior to oxygenation by ECMO.

Most commonly, oxygen saturation (measured by oximetry or blood gas analysis) has been used to calculate recirculation in Formula 2 (13). The main limitation of this method is the difficulty in measuring the mixed venous oxygen (i.e. prior to oxygenation by the ECMO circuit), because of the differing oxygen content in the SVC and IVC (13, 14).

Van Heijst et al. (2001) suggested that the most accurate technique for estimating mixed venous oxygen in ECMO patients (13) is to temporarily cease ECMO sweep gas flow and use the ventilator to achieve an arterial oxygen saturation equivalent to that achieved on ECMO support. The oxygen saturation of blood in the venous drainage cannula (measured using oximetry) would represent the true mixed venous oxygen saturation. While this technique is more accurate than central venous measurement of oxygen saturation, it is time-consuming, prone to measurement error and may not be tolerated in highly ECMO-dependent patients (13).

However, because blood that is highly oxygenated by ECMO also has higher levels of dissolved oxygen, measurement of recirculation using oxygen content may be more accurate. This has been demonstrated in animal and in vitro studies (14, 15). However, other authors have argued that in clinical settings, where oxygen saturation is typically below 95%, the contribution of dissolved oxygen is negligible and therefore saturation is appropriate for use in recirculation formulae (10).

Lindstrom et al. (2009) developed an alternative strategy to assess recirculation, based on oxygen content measurements in a dog on cavo-atrial VV-ECMO (14). Using a bypass loop to create a known level of recirculation, they found that measurement of recirculation using oxygen content had an excellent correlation with true recirculation \((r^2 = 0.89)\) (with a bias of +18.6%), which was more accurate than measurement using oxygen saturation.

**Dilutional ultrasound**

Dilutional ultrasound is based on changes in ultrasound velocity in response to saline injection. Ultrasonic flow sensors are placed on the access and return cannulae. Injecting a saline bolus into the return cannula changes the velocity properties of ultrasound, producing a ‘dilution curve’. Recirculated saline subsequently generates a second dilution curve, which is detected by the ultrasonic probe on the access cannula. The ratio of the areas under the two dilution curves then determines the recirculation fraction (Formula 3) (16).

\[
\text{Recirculation} (%) = \frac{S_{\text{access cannula}}}{S_{\text{return cannula}}} \times 100\%
\]

Formula 3: Recirculation formula for dilutional ultrasound. \( S \), area under the curve.
This technique was first validated in the measurement of arteriovenous fistula recirculation in hemodialysis patients (17). Since then, several studies have investigated its use in VV-ECMO (13, 16, 18-20). Van Heijst et al. (2001) and Darling et al. (2006) conducted animal trials of VV-ECMO, but found no significant difference between recirculation calculated using dilutional ultrasound versus the standard recirculation formula (13, 16). Clements et al. (2008) reported the first use of dilutional ultrasound for measuring recirculation in a neonate and noted considerable changes in recirculation over time (range 15-57%), especially with patient movement (18). Korver et al. (2012) used dilutional ultrasound to demonstrate increased recirculation fractions (45% and 38%) in two patients with a malpositioned dual lumen cannula, reinforcing the potential of this technique in monitoring VV-ECMO patients (20). Similarly, Gehron et al. (2014) measured recirculation fractions of 25-30% in five VV-ECMO patients, although this level of recirculation did not adversely affect their level of oxygenation (19).

Other applications of dilutional ultrasound in VV-ECMO have also been examined. Using the principles of the standard recirculation formula based on oxygen saturation, Walker et al. (2009) used recirculation values derived from ultrasound dilution to calculate true mixed venous saturation (15). A blood-based mock circulation loop was used with a fixed recirculation fraction. However, significant differences in actual versus calculated mixed venous saturation were found at systemic oxygen saturations above 60%. In common with other authors (12), they concluded that the standard recirculation formula is inaccurate if oxygen saturation is used, and in a subsequent study, demonstrated improved accuracy if oxygen content was used instead (21). However, further human studies are needed to validate the use of dilutional ultrasound in patients on VV-ECMO.

**Thermodilution**
Thermodilution can be used to measure recirculation by injection of a saline bolus into the return line and measurement of the temperature-time curve in the access line (11). Using a rabbit model with dual-lumen cannulation, Sreenan et al. (2000) demonstrated a positive correlation between recirculation and ECMO pump flow ($r = 0.9, p<0.005$) (11). Limitations of this study included the use of only one recirculation fraction (100%) as a reference standard, and the observation of a second peak in recirculation with ECMO pump flows under 150mL/minute (for unknown reasons). This method for measuring recirculation has also not been validated in humans.

**Lithium dilution**
An in-vitro study by Linton et al. (1998) described a lithium dilution technique for determining recirculation, using a mock circulation loop (22). Lithium chloride was injected in the return line, and concentration-time curves recorded in the access and return lines. While this technique showed good correlation with true recirculation values, it has clinical limitations of cost, availability and lack of validation in humans (14).

**Threshold for clinically significant recirculation**
Following VV ECMO cannulation, gross recirculation can be detected clinically by visual examination of the drainage and return lines. This should be excluded before the cannulae are secured in position. In our experience, the drainage and infusing lumens should be at least 10cm apart. For double-lumen cannulae, we have also observed more recirculation when the infusing lumen is in the lower right atrium (closer to the IVC) than when it is in the mid or upper right atrium.

However, there is currently no standard definition of clinically significant recirculation, which is likely in part due to the challenges of accurate measurement. Previous authors have suggested that a recirculation fraction of 20-30% is of clinical importance (23).

Locker et al. (2003) proposed a simple bedside method for excluding clinically significant recirculation using arterial blood gas (ABG) analysis, rather than quantifying recirculation (23). ABG measurements were taken from the ECMO drainage and return cannulae of 10 patients on femoro-atrial VV-ECMO. The authors suggested that a venous PO$_2$ within the physiologic range and below 10% of arterial PO$_2$ was sufficient to exclude any clinically significant recirculation. Key limitations of this study, however, included its small size, investigation of only femoro-atrial VV-ECMO (as opposed to femoro-femoral VV-ECMO, which is associated with higher recirculation fractions) and lack of patients with clinically significant recirculation for comparison.

Sidebotham et al. (2012) suggested that in clinical practice, a high oxygen saturation (>75%) in the ECMO draining (pre-oxygenator) cannula combined with a low patient oxygen saturation (<85%) indicates significant recirculation (24). The authors further suggested that recirculation could be assessed by comparison of pre- and post-oxygenator PO$_2$. A pre-oxygenator PO$_2$ of less than 10% of the post-oxygenator PO$_2$ suggested that significant recirculation was unlikely, although these clinical techniques have not been validated.

**Techniques for Reducing Recirculation**

The majority of strategies suggested for minimizing recirculation have been centered on cannulation configurations and positioning in VV-ECMO. Other factors known to influence recirculation, such as ECMO flow rate, may also be modulated.

**Cannula separation**

Togo et al. (2015) examined recirculation in relation to separation of the access and return cannula tips in a goat model of femoro-jugular VV-ECMO (12). Recirculation was lowest when the access and return cannula tips were located furthest apart in the IVC and SVC, respectively. Conversely, recirculation was highest when the cannula tips were close together in the IVC.

If recirculation is suspected in this cannula configuration, transesophageal echocardiography or fluoroscopy can be used to guide withdrawal of either cannula to increase the separation between them (24). However, no standardized recommendations exist regarding the ideal separation between the access and return cannulae. Suggested insertion techniques have included the
use of echocardiographic and pressure guidance (25-27).

**Dual lumen cannula**

Introduced for adult use in 2008, the dual-lumen cannula has been designed to minimize recirculation between the access and return lumens (28). However, there is limited evidence on recirculation in these cannulae in humans.

Van Heijst et al. (2001) measured recirculation using ultrasound dilution in a lamb model of VV-ECMO with a dual-lumen cannula (13). Recirculation increased with higher ECMO flow rates, from 13.0±4.0% at 50mL/kg/min to 36.0±12.8% at 150mL/kg/min. These values correlated well with oxygen saturation calculations (r=0.68, p<0.01). Also using oxygen saturation calculations, Okamoto et al. found in dogs that recirculation increased from 1.5% at ECMO flows of 10ml/kg to 12.8% at 40mL/kg (6). Similarly, Wang et al. (2008) found in cattle that recirculation was as low as 2%. However, overall recirculation averaged 10-30% over 15 days at low ECMO flows of 2L/min, a wide variation which may have been partly due to cannula malpositioning (29).

Human trials have demonstrated the safety and efficacy of oxygenation with dual lumen cannula, though none have specifically measured recirculation (30-33). Hence there remains insufficient evidence to support the superiority of dual-lumen cannulae in reducing recirculation, compared to conventional two-cannulae configurations. Studies using three-dimensional computational fluid dynamics may help to improve future dual-lumen cannula designs (34).

**Alternative cannulation configurations**

A variety of ECMO cannula configurations have been examined in humans. Rich et al. (1998) demonstrated that femoro-atrial VV-ECMO (access flow from the right femoral vein, return flow to the right atrium via the superior vena cava) provided higher pulmonary arterial mixed venous oxygen saturation, compared to the reverse configuration (35). Ichiba et al. (2000) described a three-cannula technique, with access cannulae in the right internal jugular and femoral vein, and return flow to the inferior vena cava via the contralateral femoral vein (36). Increased oxygenation and ECMO flow rates were observed after insertion of the second drainage cannula. These improvements were in part attributed to the adequate separation of the access and return cannula tips, minimizing recirculation and thereby improving oxygenation.

Lin et al. (2009) suggested a modification to the ECMO return cannula to better direct the infusing jet stream toward the tricuspid valve and right ventricle, reducing recirculation by increasing separation between the access and return cannula (37). A suture was passed through the return cannula (prior to placement) to alter its curvature. This modification improved oxygenation in a patient who had persistent hypoxemia refractory to repositioning of the ECMO cannulae.

Bonacchi et al. (2011) described a chi-configuration with a similar modification to the return cannula, which was positioned with its tip just proximal to the tricuspid valve and overlapping the access cannula (5). The access cannula had
two ports draining the SVC and IVC respectively. This technique was subsequently associated with significantly lower recirculation, compared to conventional femoro-jugular VV-ECMO (5.31±3.68% versus 29.43±8.96%, p<0.0001).

Lindstrom et al. (2012) examined veno-ventricular cannulation for VV-ECMO in a dog model, in which the tip of the return cannula was placed in the right ventricle (38). Compared to femoro-jugular cannulation, this configuration significantly reduced recirculation (8.4% versus 37.9% at 4L/min, p<0.01). Furthermore, the typical increase in recirculation seen at higher ECMO flow rates was consistently lower for veno-ventricular VV-ECMO than for femoro-jugular VV-ECMO (2.9% per L/min versus 11.1% per L/min, p<0.0001) (14).

**Conclusion**

Because recirculation is a common and dynamic event during VV-ECMO, it is essential that it is recognized and managed appropriately, as it may lead to severe hypoxaemia. Recirculation is most commonly calculated using blood oxygen saturations, although this may be less accurate than the use of oxygen content calculations. Other quantification techniques, such as dilutional ultrasound, may have a role in the dynamic monitoring of recirculation, but further human studies are required to validate their use in clinical practice. Clinically significant recirculation in patients cannulated with a two- or three-cannula configuration should be managed by increasing separation between the access and return cannulae. Dual-lumen ECMO cannulae appear to have a low recirculation fraction when correctly positioned, but are prone to increased recirculation if the cannula moves. While alternative cannulation strategies have been suggested to minimize recirculation, there is limited data on their relative efficacy and safety. More robust data from clinical and laboratory studies are needed to effectively evaluate and address this persistent complication.
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