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Chronic respiratory dialysis

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Extracorporeal carbon dioxide removal is emerging as a potential strategy to manage acute hypercapnic respiratory failure. There may be an opportunity to use similar techniques to manage chronic hypercapnic respiratory failure, in what may be termed "chronic respiratory dialysis", potentially altering

the physiological and clinical effects of chronic hypercapnia associated with certain chronic lung diseases.

The use of extracorporeal gas exchange support for respiratory failure has grown rapidly and in parallel with improvements in extracorporeal technology that have led to more efficient gas exchange with potentially more favourable risk profiles (Thiagarajan et al. 2017). This growth has predominantly come from the increased use of extracorporeal membrane oxygenation (ECMO) for the most severe forms of the acute respiratory distress syndrome (ARDS) (Karagiannidis et al. 2016). However, there is an evolving interest in the use of extracorporeal carbon dioxide removal ($ECCO_2R$) for both acute and chronic respiratory failure (Deniau et al. 2016; Morelli et al. 2017), with a current focus on its potential to facilitate the minimisation or avoidance of invasive mechanical ventilation and its associated consequences (Abrams and Brodie 2013). As the technology continues to evolve, the question arises as to whether $ECCO_2R$ could play a role in the management of chronic hypercapnic respiratory failure by decreasing the respiratory load in patients with advanced lung disease.

Differences between ECMO and $ECCO_2R$

Although technically consisting of the same circuit components as ECMO (e.g. cannulae, tubing, gas exchange membrane, and most frequently incorporating a centrifugal pump), the difference between ECMO and $ECCO_2R$ is that the intention of $ECCO_2R$ is specifically carbon dioxide removal without emphasis on oxygenation, whereas ECMO is intended to provide both carbon dioxide removal and significant oxygenation—a distinction that has important clinical implications. Oxygenation is, in large part, dependent on the amount of extracorporeal blood flow in order to saturate a sufficient amount of haemoglobin. This typically necessitates the use of large cannulae to achieve adequate blood flow to meet the needs of patients with severe hypoxaemia (Schmidt et al. 2013). In contrast, carbon dioxide removal is much more efficient than oxygenation, allowing for the use of lower blood flow rates than in ECMO, potentially even within the range of what may be used for continuous venovenous haemodialysis (CVVH), though without significant contribution to oxygenation. With less demand for blood flow, $ECCO_2R$ can be achieved with smaller cannulae, comparable to dialysis catheters, which may have an improved risk-benefit profile compared to ECMO (Morelli et al. 2017). Additional modalities that are being explored to further optimise the efficiency of $ECCO_2R$, by maximising the gradient of carbon dioxide across the membrane, include the use of electrodialysis, blood acidification and carbonic anhydrase (Arazawa et al. 2012; Zanella et al. 2015; 2014).

$ECCO_2R$ devices

The derivation of $ECCO_2R$ devices has come from several directions—downsizing of circuits originally intended for ECMO in order to accommodate lower blood flow rates (e.g. Novalung, Xenios AG, Heilbronn, Germany); modifications to circuits intended for CVVH (e.g. PrismaLung, Baxter, Illinois, USA); and devices designed specifically for the intention of providing ECCO2R (e.g. Hemolung RAS, ALung, Pennsylvania, USA). Conceptually similar, each of these devices may have circuit-specific advantages and risks, with no single device as yet proving to be superior for carbon dioxide removal over another. Several of these devices are being used as part of prospective, randomised controlled trials of ECCO2R for various aetiologies of acute respiratory failure (Fanelli et al. 2016; McNamee et al. 2017).

Potential uses of $ECCO_2R$

In theory, $ECCO_2R$ can be used for any clinical scenario in which the goal is extracorporeal management of ventilation, and when oxygenation is supportable by other means. An area of active investigation is ECCO2R for ARDS in order to facilitate reductions in tidal volumes, plateau airway pressures, and respiratory rates to minimise the extent of ventilator-associated lung injury (VALI) (Abrams and Brodie 2013; Bein et al. 2013; Fanelli et al. 2016; Grasso et al. 2014; Terragni et al. 2009). Beyond ARDS, and perhaps the more obvious target of carbon dioxide removal is the potential role of $ECCO_2R$ in acute hypercapnic respiratory failure, such

as may be encountered in acute exacerbations of chronic obstructive pulmonary disease (COPD), cystic fibrosis, and severe status asthmaticus, among others. $ECCO_2R$-facilitated correction of respiratory acidosis has been shown to be feasible in patients with acute hypercapnic respiratory failure in the setting of COPD exacerbations that has either not responded to noninvasive ventilation (NIV), or has persisted despite invasive mechanical ventilation (Abrams et al. 2013; Del Sorbo et al. 2014; Kluge et al. 2012). $ECCO_2R$, through correction of the respiratory acidosis, may reduce the work of breathing (which, in turn, reduces the production of carbon dioxide by the respiratory muscles, decreasing the overall carbon dioxide load to be excreted) (Cardenas et al. 2009; Diehl et al. 2016), dynamic hyperinflation, and potentially the need for ongoing mechanical ventilatory support, in turn facilitating early mobilisation and rehabilitation and avoiding the complications of ventilator-associated pneumonia and worsening hyperinflation (Abrams et al. 2013). Similarly, $ECCO_2R$ has been used for acute hypercapnic respiratory failure in the setting of advanced chronic lung disease as a bridge to lung transplantation, often with the ability to avoid invasive mechanical ventilation prior to transplantation (Biscotti et al. 2017; Fuehner et al. 2012).

$ECCO_2R$ may be capable of correcting hypercapnic respiratory failure in the acute settings, but what about in the chronic setting as a means of consistently resetting carbon dioxide levels in patients with decreased ventilatory capacity from chronic lung disease? In this context, carbon dioxide removal could function as a form of chronic respiratory dialysis (Ranieri et al. 2017).

Carbon dioxide is stored in several forms within the body, the vast majority of which is as bone carbonate (very slowly exchanged) and bone bicarbonate (slowly exchanged) (Cherniack and Longobardo 1970). The remaining carbon dioxide is stored as blood bicarbonate, dissolved gas in plasma, carbamino compounds within erythrocytes, and free gas within alveoli, all of which is more readily exchanged. If an $ECCO_2R$ -like device could remove carbon dioxide at a rate and frequency that would allow for meaningful reductions in carbon dioxide stores that are not typically accessed, it may be theoretically feasible to recalibrate the baseline plasma carbon dioxide levels in patients with chronic hypercapnic respiratory failure. By decreasing the ventilatory requirements in patients with already limited ventilatory capacity, such a device might sufficiently reduce the work of breathing, the respiratory load and the amount of carbon dioxide produced, as well as facilitate improvement in the hyperinflation and gas trapping that increases dead space and puts respiratory muscles at a mechanical disadvantage (McKenzie et al. 2009; Tobin et al. 2009).

While theoretically this has the potential to be a therapeutic option, there are many aspects of chronic respiratory dialysis that require further investigation prior to any consideration of clinical application. Most importantly, there needs to be a better understanding of the kinetics of carbon dioxide exchange, particularly in regards to the rate of exchange between blood and bone or other stores of carbon dioxide (Cherniack and Longobardo 1970). This relationship will help inform the frequency and intensity of $ECCO_2R$ that would need to be applied on a chronic basis to have a meaningful effect on carbon dioxide levels. Mathematical modelling and physiological studies would be helpful in providing this information.

Secondly, in whom should chronic respiratory dialysis be considered? Patients with COPD with chronic hypercapnic respiratory failure have shown variable responses to the chronic use of NIV on blood carbon dioxide levels and exacerbation rates (Elliott et al. 1991; Meecham Jones et al. 1995; Murphy et al. 2017; Ramsay and Hart 2013; Struik et al. 2014). The discrepancy in findings from two randomised controlled trials of NIV for the management of hypercapnia that persisted after acute exacerbations of COPD highlights an important point regarding the potential use of carbon dioxide removal for the management of chronic hypercapnia (Murphy et al. 2017; Struik et al. 2014). NIV may be effective in maintaining long-term control of hypercapnia in some patients and is clearly a less invasive approach than carbon dioxide removal (Ramsay and Hart 2013). However, there are patients within this population who are non-responders to long-term NIV management, particularly as it relates to control of hypercapnia, and perhaps would be suitable for chronic respiratory dialysis as an alternative. The data for efficacy of NIV for the management of hypercapnia in cystic fibrosis and other forms of bronchiectasis are limited to small trials with inconsistent results (Moran et al. 2017). Select patients within these populations who are non-responsive to or intolerant of NIV may likewise be considered potential candidates for chronic respiratory dialysis.

Identifying the appropriate subset of patients that should be studied will require further analysis of existing data and prospective trials that are ideally enriched with patients most likely to respond to the use of chronic carbon dioxide removal based on physiologic and other predictive factors. This type of modelling has been proposed in the acute setting (Goligher et al. 2017; Lindberg et al. 2017). There are also practical applications that should be considered, including how one would actually physically initiate carbon dioxide removal and whether this might influence the target population for further study. Patients with chronic hypercapnic respiratory failure and end-

stage renal disease who receive haemodialysis through tunnelled catheters or arteriovenous fistulae or grafts would have pre-existing access that might be suitable for the application of carbon dioxide removal. To that end, future iterations of carbon dioxide removal technology might be combined with renal dialysis machines, facilitating the performance of both processes simultaneously (Forster et al. 2013; Husain-Syed et al. 2016; Quintard et al. 2014; Romagnoli et al. 2016). However, the convenience of studying such a patient population may be offset by the coexisting burden of comorbidities that may negatively impact any long-term benefit gained from chronic respiratory dialysis. Instead, if patients were to require dedicated access for carbon dioxide removal, one must consider what form that would take—tunnelled catheter, fistula, graft—and whether that access would be appropriate to sustain the low blood flow rates typically used for $ECCO_2R$.

Conceptually, the idea of intermittent $ECCO_2R$ for chronic hypercapnic respiratory failure does not differ to any great degree from a hypothetical destination device for the support of severe, end-stage respiratory failure from other aetiologies, a so-called artificial lung, which could likewise be referred to as ‘chronic respiratory dialysis’. The main practical differences would be the intermittent versus continuous use of the device, and whether carbon dioxide removal alone, or both carbon dioxide removal and oxygenation are needed, which would have significant implications for the amount of blood flow needed and the type and source of gas supplied.

When considering chronic respiratory dialysis, special attention will need to be paid to its effect on the physiology of gas exchange. A carbon dioxide removal device that removes a considerable amount of carbon dioxide while contributing a negligible amount to oxygenation may have unanticipated consequences for oxygenation. Imagine that fifty percent of the total body carbon dioxide production is removed by the device, with unchanged oxygen transfer by the patient's native lungs. The respiratory exchange ratio of the native lungs would then be reduced by half, to approximately 0.4 (from a normal value of 0.8). According to the alveolar gas equation, the partial pressure of oxygen in the alveolus would reach unacceptably low levels, and an enrichment of the inspired fraction of oxygen would become necessary.

Economic considerations

In addition to the clinical implications, one must consider the potential economic impact of such a strategy on, potentially, a very large patient population for a long period of time, much in the way haemodialysis has impacted patients with advanced renal failure (Li et al. 2017). Aside from the cost of the technology itself, the potential of increasing the life expectancy of patients known to have multiple comorbidities (e.g. cardiovascular disease) may substantially increase overall healthcare costs (Wacker et al. 2017).

What constitutes success?

Lastly, there is no consensus on what constitutes success of chronic respiratory dialysis. Normalisation of the carbon dioxide in a chronic respiratory acidosis may be achievable as a physiological endpoint, but it must also demonstrate improvement in clinically meaningful outcomes for it to have any role in clinical practice. Quality of life, exercise capacity, rate of exacerbations, and mortality would all be appropriate endpoints for future studies, accompanied by the applicable cost-benefit analyses.

Conclusion

In conclusion, advances in extracorporeal gas exchange have created an opportunity to intervene upon both acute and chronic hypercapnic respiratory failure. A better understanding of the physiology behind carbon dioxide metabolism and how that might impact the application and effectiveness of chronic respiratory dialysis is needed in order to understand which patients might benefit from this potential therapeutic strategy.

Conflict of interest

Daniel Brodie is currently the co-chair of the Trial Steering Committee for the VENT-AVOID trial sponsored by

ALung Technologies. He was previously on the medical advisory board of ALung Technologies and Kadence (Johnson & Johnson). All compensation for these activities is paid to Columbia University. Darryl Abrams and Antonio Pesenti declare that they have no conflict of interest.

Abbreviations

ARDS acute respiratory distress syndrome

COPD chronic obstructive pulmonary disease

CVVH continuous venovenous dialysis

ECCO2R extracorporeal carbon dioxide removal

ECMO extracorporeal membrane oxygenation

NIV noninvasive ventilation

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