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# Relatively Increased $CO_2$ Delivered to the Brain From the Descending Aorta Leading to an Elevated Respiratory Rate Causing Differential Hypocapnia (RIDDLER or East-West Syndrome): New Pitfalls in Awake Peripheral V-A ECMO

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Veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) is increasingly used worldwide in patients with cardiogenic shock/arrest with severe biventricular failure, often combined with oxygenation/ventilation failure.[1] Broadly, 2 forms of V-A ECMO support are distinguished: central and peripheral. The central configuration involves direct access to the great vessels through the open chest and is associated with a higher rate of complications (bleeding, infections, etc), so this is typically reserved for patients after cardiotomy. The peripheral V-A ECMO configuration is most frequently used,[1] with the femoral artery returning oxygenated blood to the systemic circulation in the vast majority of these circuits. This results in blood flowing in the opposite direction to normal physiological conditions (retrograde flow) along almost the entire aorta.

When cardiac recovery precedes pulmonary recovery, the heart will start to eject poorly oxygenated blood against the retrograde blood flow from the ECMO pump. A similar situation can be seen when cardiac offloading is facilitated in V-A ECMO with active unloading devices like Impella in the "ECPELLA configuration." The end result is that the upper body supplied by vessels leaving the proximal aorta can become relatively hypoxic and cyanosed compared with the parts of the lower body (supplied by the distal aorta) that is well-oxygenated by the ECMO circuit, extensively described in the literature and known as Harlequin syndrome or North-South syndrome.[2] This is the main reason to continuously monitor the patient's oxygenation status at the level of the right upper limb and through bilateral cerebral tissue oximetry.[3]

With increasing experience in mechanical circulatory support, the concept of "awake V-A ECMO" is gaining more traction to prevent ventilator-associated pneumonia, delirium, and intensive care unit acquired weakness.[4] This growing enthusiasm for awake peripheral V-A ECMO brings new challenges and pitfalls for the intensive care unit physician, and one should always keep in mind the concept of differential hypocapnia. As an illustrative example, we present the following case. A 39-year-old patient with fulminant myocarditis, supported by peripheral ECMO plus Impella 5.5, was extubated to enable early physiotherapy. The right radial blood gas showed a pH of 7.42, Pao2 of 75 mm Hg (9.6 kPa), and Paco2 of 42 mm Hg (5.6 kPa). The patient soon became delirious, and it was suspected that he aspirated his feed as he developed an elevated respiratory rate at 22/min. The subsequent right radial blood gas showed a pH of 7.51, Pao2 of 67 mm Hg (8.9 kPa), and Paco2 of 32 mm Hg (4.3 kPa), so it was mistakenly thought that the ECMO sweep was set too high, and it was gradually reduced. The tachypnea worsened,

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leading to the patient being sedated and reintubated for a presumed aspiration pneumonitis. However, the first postoxygenator blood gas showed significantly elevated Paco2 levels of around 60 mm Hg (8 kPa). This physiological process is illustrated with the following steps (Figure).

1. The spontaneous ventilating patient develops a mild tachypnea as an appropriate response to exertion, pain, sepsis, etc.
2. The increase in minute volume will result in their lungs clearing more $CO_2$. That decarboxylated blood from the lungs (indicated in green) will reach the right brachiocephalic trunk, but may not reach all of the cerebral circulation because of the weakened heart's inability to overcome the retrograde flow of blood from the peripheral ECMO circuit. Blood sampled from the right arm has a low $CO_2$ and high pH.
3. The ECMO clinician will be inclined to decrease $CO_2$ clearance by the ECMO circuit by decreasing the device's gas sweep.
4. This results in an increasingly hypercapnic retrograde blood flow from the ECMO circuit to the aortic arch (indicated in red), where it enters the cerebral circulation, and respiratory drive centers through the left common carotid artery.
5. Increasingly hypercapnic ECMO blood flow to the brain results in an inappropriate further increase in the respiratory rate, increasing the minute volume of the spontaneously ventilated patient even more. This results in a seemingly paradoxical further reduction of $Paco_2$ measured in the right radial artery, despite the reduction in $CO_2$ clearance by the ECMO device.
6. The ECMO clinicians continue to respond to the decreasing $Paco_2$ in the right radial artery with

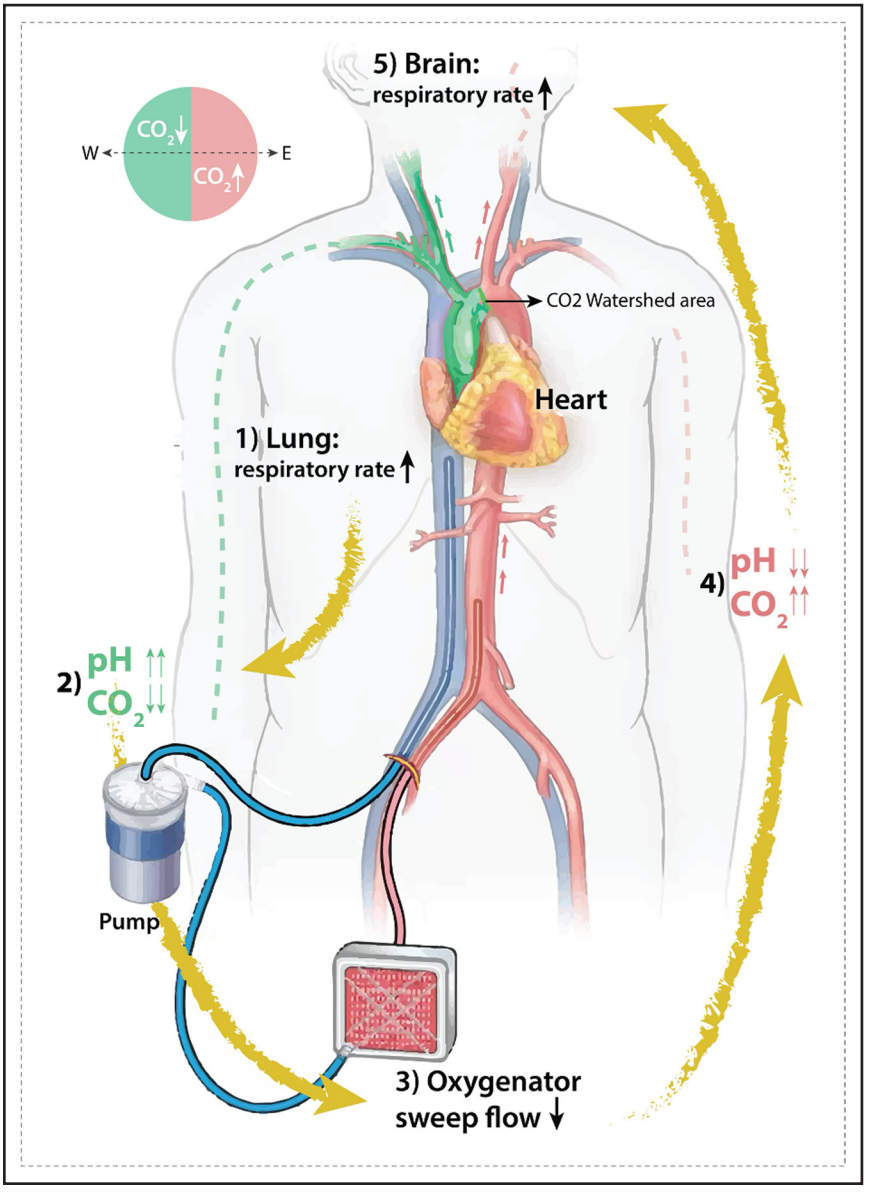


**Figure.** Illustration of the step-by-step physiological process of relatively increased $CO_2$ delivered to the brain from the descending aorta leading to an elevated respiratory rate causing differential hypocapnia (RIDDLER) or East-West syndrome in awake peripheral veno-arterial extracorporeal membrane oxygenation–supported patients.

further reductions in the ECMO sweep gas, resulting in a vicious cycle for worsening cerebral hypercapnia with paradoxical tachypnea.

We identify this process as differential hypocapnia, and in analogy to differential hypoxia, we propose for the first time the term East-West syndrome or relatively increased $CO_2$ delivered to the brain from the descending aorta leading to an elevated respiratory rate (RIDDLER) syndrome.

It is important to recognize this syndrome early, because this iatrogenically induced vicious cycle can quickly lead to respiratory exhaustion, worsening cerebral edema, and neurological injury (Figure).[5] When RIDDLER syndrome is suspected, the central, mixed venous, and postoxygenator $Pco_2$ measurement (or an additional left radial arterial line) can be used to gain valuable data about global $CO_2$ kinetics and aid clinical decisions around the optimal ventilatory and ECMO settings required for decarboxylation. In addition, the location of the watershed area (the meeting point of antegrade and retrograde blood flow) can potentially be located within the aorta by echocardiography.[3]

The treatment of RIDDLER syndrome requires an understanding of the complex physiology at play on mechanical circulatory support, and instead of intuitively lowering the sweep gas flow, decarboxylation should be monitored using post-oxygenator $CO_2$/pH measurements rather than right radial blood gas measurements. Matching the sweep gas to the blood flow in a 1:1 ratio is a useful starting place once in the maintenance phase of V-A ECMO therapy and aiming for physiologically normal pH and $Pco_2$ in the postoxygenator/left radial arterial blood gases. This will prevent or break the vicious cycle of increasing hyperventilation and result in the normalization of the right radial $Pco_2$ and pH. It is important to consider potential underlying causes of tachypnea and treat them accordingly; this may include the use of pain relief, anxiolytics, light sedation, nasal high-flow or noninvasive ventilation. In the case of concomitant respiratory failure and differential hypoxia (re) intubation, ventilation, sedation, and even neuromuscular blockade may be required.

To conclude, we have observed clinically significant regional hypocapnia as a cause of seemingly unexplained respiratory distress in patients supported with awake peripheral V-A ECMO; we have named this pathology RIDDLER or East-West syndrome, a clinical entity distinct from the differential hypoxemia that is frequently seen in peripheral V-A ECMO patients with Harlequin syndrome and requires a very different management strategy to prevent respiratory distress. Clinicians should remain vigilant for the effects of both Harlequin and RIDDLER syndromes when supporting spontaneously ventilating patients on peripheral V-A ECMO.

## ARTICLE INFORMATION

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