Is fluid overload a target to treat sleep disordered breathing in patients with end-stage renal disease, and what are the underlying mechanisms?

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Sleep problems are more common in patients with renal failure compared to populations without overt severe comorbidities. Both central and obstructive forms of sleep disordered breathing (SDB) are present in patients with renal failure [1, 2]. Other sleep problems, including restless leg syndrome, periodic limb movement syndrome and insomnia, also occur at high rates in this population. As the severity of renal impairment increases so too does the prevalence and severity of sleep disorders [3, 4]. Indeed, in end-stage renal disease, significant SDB (apnoea–hypopnoea index ⩾15 per hour sleep) can occur in up to 70% of cases, regardless of whether such patients are on haemodialysis or peritoneal dialysis [5, 6].

Depending on the severity of disease, prior to or in conjunction with implementation of specific therapies for SDB such as positive airway pressure, attempts to alleviate SDB with recommendations such as weight loss, cessation of alcohol consumption, as well as treatment of the underlying disease that may worsen SDB are justified. To direct treatment of SDB in patients with end-stage renal failure it is crucial to increase understanding of the underlying pathophysiology of SDB in this patient population.

In this context, in a study published in this issue of the *European Respiratory Journal*, Lyons *et al.* [6] evaluated whether in patients with end-stage renal disease, one of several diseases characterised by fluid overload, the presence of sleep apnoea is associated with greater body extra cellular fluid volume as well as neck, thorax and leg fluid volumes. Specifically, the authors studied 42 non-obese patients with end-stage renal disease on thrice-weekly haemodialysis [6]. 67% had an at least moderately severe sleep apnoea (apnoea–hypopnoea index ⩾15 events per hour sleep) the night following a non-dialysis day. The sleep apnoea and no sleep apnoea groups were similar with respect to the frequency and severity of heart disease, the frequency and efficiency of haemodialysis, and body mass index, which on average was within the normal range (24.3 *versus* 22.9 $kg \cdot m^{-2}$). Nevertheless, the sleep apnoea group had significantly higher

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evening extracellular volume indices for total body (Δ 0.9 $L \cdot m^{-2}$), legs (Δ 0.148 $L \cdot m^{-2}$), thorax (Δ 0.370 $L \cdot m^{-2}$) and neck (Δ 0.039 $L \cdot m^{-2}$) compared to the no sleep apnoea group [6]. Importantly, in a multivariable linear regression analysis including potential modulators of the severity of sleep apnoea (apnoea–hypopnoea index), extracellular fluid volume was the only independent modulator of the apnoea–hypopnoea index (r=0.468, p=0.002), whereas body mass index was not [6]. In the context of previous evidence, these data are consistent with the concept that fluid overload contributes to the pathogenesis of SDB or when already present may perpetuate its severity.

While the study described by LYONS *et al.* [6] clearly adds to the increasing body of knowledge on this topic, the cross-sectional, non-intervention design and other methodological considerations limit the ability to make cause and effect conclusions. The study also highlights the need for further investigation with appropriately designed studies in this patient population to address important questions regarding underlying mechanisms. Some of the methodological considerations and unanswered mechanistic questions are briefly summarised below.

There are at least four key pathophysiological traits (or phenotypes) that contribute to the development of obstructive sleep apnoea (OSA) [7, 8]. These include a narrow or collapsible pharyngeal airway and non-anatomical contributors such as unstable respiratory control (high loop gain), inadequate activation of the pharyngeal dilator muscles during sleep (poor muscle responsiveness) and premature awakening to minor airway narrowing (low respiratory arousal threshold) (figure 1). There is clear overlap in pathophysiology of obstructive and central apnoea [9]. For example, unstable respiratory control is a feature of both forms of SDB [9]. Upper airway narrowing also occurs during central apnoea [10]. Fluid overload may increase the propensity for unstable respiratory control. Indeed, chemosensitivity is heightened in patients with heart failure and end-stage renal disease [11, 12]. In patients with renal failure, mechanisms unique to this patient group such as uraemic destabilisation of central respiratory control may also be involved [13]. The sample size in the LYONS *et al.* [6] study was too small to draw robust conclusions with respect to whether the observed correlation with fluid overload in patients with end-stage renal disease is stronger with increasing severity of obstructive compared to central sleep apnoea or *vice versa*. Thus, this will require further investigation in a larger cohort and may provide insight into the potential relative importance of this mechanism in driving each form of SDB in these patients. Ultimately however, direct measurements of overall respiratory control (*e.g.* loop gain) [14, 15] and other components of respiratory control (*e.g.* CO_2 reserve/apnoea threshold) during sleep using gold standard methodology or accurate surrogate estimates [16] are required in this population to determine the relative contribution of unstable respiratory control definitively. This line of investigation has the potential to identify new targets for therapy.

Fluid overload leading to greater accumulation in the neck when supine may also increase upper airway collapsibility. Indeed, awake assessments of upper airway collapsibility in acute fluid redistribution intervention studies provide support for this mechanism [17, 18]. However, awake assessments of collapsibility involve multiple mechanisms beyond the passive anatomical characteristics of the airway (*e.g.* neuromuscular and

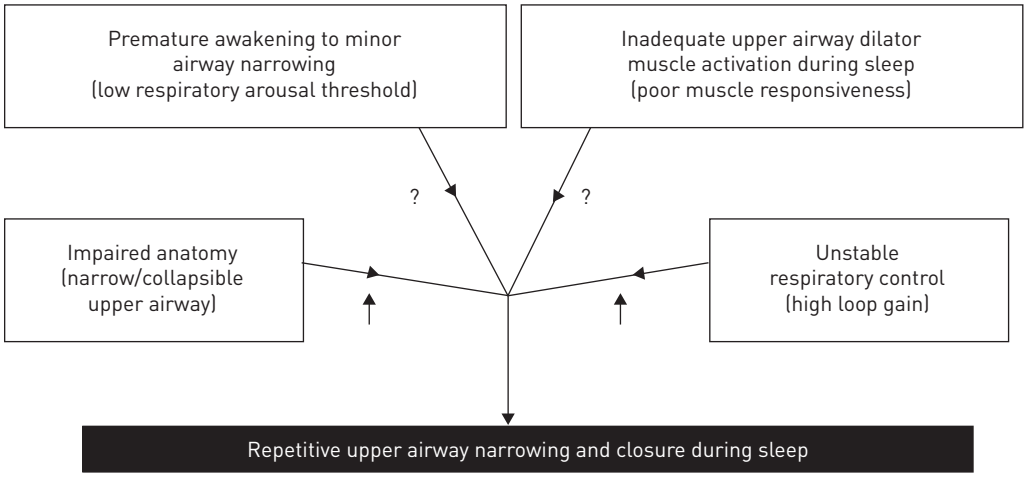

FIGURE 1 Schematic of the four key pathophysiological traits (or phenotypes) that cause sleep apnoea and the potential mechanisms by which fluid redistribution may contribute to sleep disordered breathing in patients with renal failure (adapted from [8] with permission). Note: increased upper airway collapsibility and unstable respiratory control (high loop gain) are the most likely contributing mechanisms whereas major changes in muscle responsiveness and the respiratory arousal threshold are less likely to be involved. However, direct assessments during sleep of the phenotypic traits that cause sleep apnoea in patients with renal failure have not been performed.

behavioural/voluntary input). Thus, quantification of upper airway collapsibility using the gold standard passive Pcrit technique during sleep [19, 20] is required in order to determine the precise role that neck fluid accumulation has on increasing upper airway collapsibility. This will also provide insight into the magnitude of the effect and allow for comparison with other established interventions that are known to reduce upper airway collapsibility and OSA severity (*e.g.* oral devices and supine avoidance) [21, 22].

Fluid accumulation is unlikely to alter the neural drive to the upper airway dilator muscles (upper airway muscle responsiveness). However, reductions in cross sectional area may diminish the ability of the pharyngeal dilators to restore airflow when challenged during airway narrowing. These potential mechanisms could be assessed using the active Pcrit technique combined with electromyography of the pharyngeal muscles [7, 8, 20]. Finally, fluid accumulation is unlikely to alter the propensity for awakening to airway narrowing (respiratory arousal threshold). However, it is of interest that most studies that have contributed to the evidence for volume overload and nocturnal rostral fluid shift as a contributor to the severity of sleep apnoea have included normal weight participants [13, 23, 24]. The causes of OSA differ between obese and non-obese individuals. Indeed, recent evidence suggests that non-anatomical contributors, such as a low respiratory arousal threshold, may be a particularly important contributor to OSA in non-obese people [25]. This remains to be tested in the context of SDB in patients with renal failure.

A final methodological consideration for study reported by Lyons *et al.* [6] is that patients in the sleep apnoea group were older and included a greater proportion of men. Both male sex and ageing are key risk factors for SDB and are associated with increased upper airway collapsibility [19] and unstable respiratory control [26, 27]. While age and sex were not independent contributors to the apnoea–hypopnoea index in the univariate regression analyses, age was independently associated with the presence of sleep apnoea in the logistic regression analysis. Thus, several factors beyond fluid redistribution likely contributed to the presence of SDB in the current study.

Regardless of the underlying mechanisms, uncontrolled interventional studies indicate that reduction of fluid overload in patients with end-stage renal disease and SDB may reduce the SDB, at least in part. For example, in the absence of uraemia, treatment of steroid-responsive nephrotic syndrome led to a 50% reduction in the apnoea–hypopnoea index coupled with a 23% fall in total body extracellular water [28]. In another study in end-stage renal failure patients, haemodialysis was intensified by switching from a conventional thrice-weekly to nocturnal haemodialysis six times per week [29]. This intervention led to a 68% reduction in the apnoea–hypopnoea index in association with a significant improvement of uraemia and total body fluid volume [29]. Importantly, ultrafiltration of 2.2 L without affecting uraemia led to a 36% reduction of the apnoea–hypopnoea index [30].

In summary, the current report by Lyons *et al.* [6] contributes to the evidence that a reduction of fluid overload in patients with end-stage renal disease may reduce, at least in part, the severity of SDB in this population. Patient selection, *e.g.* patients with mild SDB or excessive fluid overload, as well as different methods to reduce fluid overload in patients with end-stage renal disease, merit further clinical evaluation. Further work into the underlying mechanisms may also yield new targets for therapy.

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