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Review

Effect of Uremia and its Treatment on Pulmonary Function

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Abstract. Alterations in respiratory drive, mechanics, muscle function, and gas exchange are frequent if not invariable consequences of uremia. Pulmonary dysfunction may be the direct result of circulating uremic toxins or may result indirectly from volume overload, anemia, immune suppression, extraosseous calcification, malnutrition, electrolyte disorders, and/or acid–base imbalances. The pulmonary system is unique because it is affected by the disease and its treatment. Acetate hemodialysis reduces alveolar ventilation and PaO_2 due to extrapulmonic CO_2 unloading. Peritoneal dialysis increases alveolar ventilation and intraperitoneal pressure. The latter leads to an elevated and lengthened diaphragm, a reduced functional residual capacity, basilar atelectasis, possible hypoxemia, and altered respiratory muscle function. In patients on chronic peritoneal dialysis, adaptations may occur that limit the reductions in lung volumes, PaO_2, and respiratory muscle strength that are often observed during acute peritoneal dialysis. This review details how uremia and dialysis interact to alter pulmonary function.

Key Words: Uremia—Pulmonary function—Peritoneal dialysis—Hemodialysis.

Introduction

Uremia refers to the clinical syndrome produced by a profound loss of renal function, whether acute or chronic. The uremic state represents a failure not only of renal excretion but also of the kidney's metabolic/endocrine function and, as such, affects virtually every organ in the body. Pulmonary dysfunction may be the direct result of circulating uremic toxins or may result indirectly from volume overload, anemia, immune suppression, extraosseous calcifica-

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tion, and/or malnutrition [26, 36, 53]. In contrast to other organs, the pulmonary system is affected both by the disease (uremia) and by its treatment (hemodialysis or peritoneal dialysis). The latter appears to have different effects depending on whether dialysate is instilled acutely or on a chronic, continuous basis. This review will examine how uremia and dialysis interact to alter pulmonary function; specifically respiratory drive, mechanics, muscle function, and gas exchange.

Respiratory Drive

Despite several studies on the regulation of breathing in uremia [2, 3, 43, 49, 51, 73, 74, 78, 90], there is little agreement. Although Alexander found respiratory sensitivity to CO_2 to be normal or increased [2], others have found it to be decreased [3, 73]. Pauli found that ventilation was better correlated to blood nonprotein nitrogen than to arterial hydrogen ion levels [74]. Sebert compared uremic patients to normal subjects and observed the former to display a significant decrease in resting minute ventilation and P-100, which was corrected by hemodialysis. Others have found ventilatory responses to CO_2 to be normal [49, 78] but respiratory load compensation to be diminished [78].

The respiratory response to CO_2 or hypoxia has not been characterized during dialysis. Extrapulmonic CO_2 unloading [32, 71] occurs during hemodialysis. However, arterial PCO_2 remains constant because of reflex hypoventilation induced by the change in venous pCO_2, pH, and/or bicarbonate levels [24, 27, 59, 85, 91, 92].

Rossing and co-workers used respiratory inductance plethysmography to demonstrate that the decrase in minute ventilation during hemodialysis (acetate buffer) results from reductions in tidal volume rather than respiratory rate [88]. Inspiratory flow rates were also reduced so that the duty cycle remained essentially unchanged [88]. De Backer observed a similar decrease in tidal volume, but noted numerous central apneas during hemodialyis [25]. The periodic breathing present during hemodialysis was not affected by sleep–wake cycles or by correction of systemic acidosis but was significantly reduced by administration of supplemental O_2 [25].

Following hemodialysis, plasma bicarbonate levels return to normal but alveolar ventilation is now inappropriately increased and a transient respiratory alkalosis occurs [10, 21, 31, 49, 87, 104]. The central nervous system's sensitivity to CO_2 is heightened, presumably by a posthemodialysis osmotic dysequilibrium syndrome [49]. When longer hemodialysis treatments are used, respiratory alkalosis and an increased sensitivity to CO_2 do not occur [43], perhaps because increased dialysis time allows for a better osmotic equilibrium [49].

In contrast to hemodialysis, significant bicarbonate unloading and consequent hypoventilation do not occur during peritoneal dialysis. Blood flow to the peritoneum does not compare with that achieved during hemodialysis, and therefore bicarbonate loss is only 13 mmol/h during intermittent peritoneal dialysis compared to 150 mmol/h during hemodialysis [32]. Thus, peritoneal

CO_2 unloading is minuscule and does not cause a reduction in alveolar ventilation. In fact, minute ventilation increases during peritoneal dialysis due to the obligatory increase in O_2 consumption and CO_2 production that results from the metabolism of the large amounts of exogenous glucose and lactate present in peritoneal dialysis solutions [35].

Respiratory Mechanics

In patients with chronic renal failure without clinical or radiographic evidence of cardiopulmonary disease, it is common to find evidence of flow limitation in small airways [76]. It is unclear if this is a direct result of uremia or a consequence of cigarette smoking, subclinical volume overload, or frequent infections. Recently, Davenport and Williams reported a 13% decrease in the peak expiratory flow rate after 30 min of hemodialysis using a cuprophan dialysate membrane [23]. This was temporally related to a decrease in the white blood cell (WBC) count, which suggests that pulmonary leukocyte aggregation may result in peribronchial edema, inflammatory mediator release, and obstructive airways dysfunction.

When restrictive pulmonary disease is present in uremic patients, it may be due to extraosseous pulmonary calcification [62, 75], vasculitis, infection, subclinical volume overload, or pleural effusions. Chronic hemodialysis itself does not affect the vital capacity unless the clinical situation is complicated by one of the above factors, most frequently volume overload and incipient cardiac failure [84].

In contrast, peritoneal dialysis does affect respiratory mechanics, largely as a result of the increase in intraperitoneal pressure that occurs with the infusion of dialysate. Berlyne and co-workers were the first to show that the decrease in vital capacity during acute peritoneal dialysis was significantly correlated with the volume of dialysate infused. This amounted to a $33 \pm 16\%$ decrease of vital capacity after 2 L infusions [7]. Plate-like atelectasis was observed in 3 of the 6 patients studied. This is presumed to be the basis for the observed decrease in PaO_2 during acute peritoneal dialysis [44].

Although these changes in pulmonary function may be of little clinical significance in the stable renal patient, they may take on critical importance in the severely ill, uremic patient with superimposed pneumonia, pulmonary edema, and anemia. If acute peritoneal dialysis is the only available option, the negative impact on pulmonary function may be minimized by reducing the volume of peritoneal dialysate infused.

During chronic peritoneal dialysis, abdominal pressure increases linearly as peritoneal volume increases over the range commonly employed: 0–3 L of dialysate [47, 76, 101]. Still unknown is whether the rise in abdominal pressure during chronic peritoneal dialysis is as great as during acute peritoneal dialysis. Consistent with the observed increase in intraabdominal pressure, most studies have shown a 10–15% reduction in functional residual capacity (FRC) after the infusion of 2 L of dialysate in chronic intermittent or continuous peritoneal

dialysis [34, 35, 47, 76, 98, 101, 102]. However, Bush and co-workers did not observe any significant change in FRC among patients on continuous peritoneal dialysis [16]. Singh measured serial changes in pulmonary function during the first 2 weeks of continuous ambulatory peritoneal dialysis (CAPD) and noted that initial reductions of vital capacity (VC), FRC, and total lung capacity (TLC) were more prominent in the supine position and returned to normal by day 15 of dialysis [95]. In patients on CAPD (2 L exchanges, 4 times/day) for more than 6 weeks, we have shown a 12 ± 2% decrease of FRC with 2 L infusion and a 20 ± 3% decrease in FRC with 3 L infusions [76]. We did not observe any significant decrease of VC as dialysate volume increased from 0 to 3 L [76].

Patients without coexistent pulmonary disease and most patients with minimal obstructive pulmonary disease are capable of tolerating CAPD [76, 95]. It remains to be seen if CAPD can be tolerated by patients with moderate to severe pulmonary dysfunction. At present, severe obstructive or restrictive pulmonary diseases are considered to be relative contraindications to peritoneal dialysis, but it is conceivable that small increases of intraperitoneal pressure and diaphragm length may acutely improve respiratory muscle strength in patients with severe hyperinflation. If peritoneal dialysis is the only treatment option available, sequential measurements of pulmonary function should be useful to identify the dialysate volume that is tolerated best.

Respiratory Muscle Function

Proximal muscle weakness is a well-known complication of chronic renal failure [39, 63, 89]. The cause is unknown but has been related to carnitine deficiency [89], vitamin D deficiency [45], parathyroid hormone excess [46], aluminum toxicity [6], and other uremic toxins [5, 67, 79]. Uremia causes type II muscle fiber atrophy [6] and alters myofibrillar ATPase, leading to reductions in myofibrillar energy utilization, creatine phosphorylation, and skeletal muscle contractility [14, 54]. Both hyperparathyroidism and hypercalcemia can interfere with mitochondrial respiration [13, 77]. In uremic rabbits, calcium uptake by the sarcoplasmic reticulum is reduced and this abnormality in excitation–contraction coupling can be reversed by vitamin D administration [50, 68]. Anemia, malnutrition, immune suppression, electrolyte disturbances, and/or acid–base imbalances can all contribute to this process.

Regardless of the cause, uremic myopathy has been shown to involve the respiratory muscles of patients with chronic renal failure receiving hemodialysis [5, 46] or peritoneal dialysis [45, 76]. Gomez-Fernandez reported the development of respiratory muscle weakness in a patient undergoing hemodialysis and its reversal after parathyroidectomy [46]. Bark and co-workers reported that maximal static inspiratory pressures (MIP) were 58.2 ± 24.9% of predicted in 10 patients undergoing hemodialysis [5]. Gomez-Fernandez and co-workers reported MIP to be similarly decreased to 59.6 ± 27.9% of predicted in 10

patients receiving chronic, intermittent peritoneal dialysis [45]. Although respiratory muscle weakness can be part of the uremic process, it is not a universal finding. Uremia is a syndrome rather than a single disease process and therefore it would be unusual for all patients to be similarly affected. Bush found MIP and maximal transdiaphragmatic pressure changes (Pdi) to be normal in 10 patients receiving chronic peritoneal dialysis [16]. We have found MIP measurements to vary considerably in CAPD patients, with the lowest measurement documented in a patient not receiving vitamin D therapy [76].

The infusion of peritoneal dialysate increases intraperitoneal pressure, elevates the diaphragm, and thereby alters the diaphragm's resting configuration. As originally proposed by Rebuck, a change in diaphragm length or radius of curvature during peritoneal dialysis might be expected to affect respiratory muscle function [83]. In order to characterize the diaphragm's in vivo force–length relationship in CAPD patients, we instilled dialysate in 1 L increments and measured lung volumes, diaphragm length [12] and radius of curvature [65] by radiographic methods, and MIP [76].

We found no significant change in either the FVC or forced expiratory volume (FEV)-1 when dialysate was added [76]. This was true even for the patients with minimal to moderate obstructive airways disease. When peritoneal dialysate volume was increased from 0 to 3 L, FRC decreased by 20% ($p < 0.001$), mean total diaphragm length index increased from 0.22 ± 0.01 to 0.28 ± 0.01 ($p < 0.001$), and diaphragm radius of curvature remained unchanged. As in other studies [16, 45], we observed a nonstatistically significant increase in respiratory muscle strength at a dialysate volume of 2 L. Only after diaphragm length was increased further by the infusion of a third liter of dialysate did we observe a statistically significant 15% increase in MIP ($p < 0.01$) and 56% increase in Pdi ($p < 0.05$).

The force–length relationship of skeletal muscle, whether limb or diaphragm, is such that optimal generation of force occurs at or near the in situ resting length (FRC) of the muscle. Maximal force occurs because at this optimal length (Lo) individual sarcomeres are at their optimal length–tension relationship. In CAPD, dialysate volume is present in the abdomen continuously, all day and all night. Due to ultrafiltration, the actual volume is closer to 3 L (drainage volume) than to 2 L (instillation volume). Both our normal subjects and our patients receiving CAPD achieved maximal inspiratory pressures at their normal resting (FRC) diaphragm length. We propose that, in patients receiving CAPD, the diaphragm has adapted to a constantly decreased FRC and increased resting length by shifting its force–length relationship to the right, so that optimal force now occurs not when the abdomen is empty but when the abdomen is filled to its chronic level.

This supports previous work in rodents showing that the diaphragm is capable of shifting or adapting its force–length relationship in response to chronic shortening (emphysema) [37, 38]. Pathologic examination in these animals showed a compensatory change in sarcomere number to preserve optimal sarcomere length–tension relationships at the new resting lung volume and diaphragm length. We postulate a similar mechanism for chronic diaphragm

lengthening in patients receiving CAPD, and we are now attempting to prove this in an animal model.

There are several alternative explanations for the improvement in diaphragm function observed in CAPD. There might be improvement in diaphragm fiber contractility as a result of the removal of "uremic toxins," the correction of electrolyte abnormalities, or improvements in patients' nutritional status. Oxygen supply might be increased by improvements in volume status or hemoglobin levels. However, these changes cannot explain the immediate improvement in respiratory muscle strength that we observed when dialysate was instilled into CAPD patients.

Furthermore, we found that increasing dialysate volume had no effect on the diaphragm radius of curvature and therefore the Laplace relationship would fail to explain the observed improvement in Pdi. Dialysate might increase abdominal impedence and thus serve as a more effective fulcrum for diaphragm contraction. The instillation of dialysate should also produce a more cephalocaudad orientation of costal diaphragm fibers, thereby allowing for a more powerful upward expansion of the rib cage during inspiration. However, if such events were significant, respiratory muscle strength would also immediately increase upon the instillation of dialysate in patients on acute or intermittent dialysis, and this does not appear to be the case [34, 47]. We suggest that only in patients receiving CAPD, in whom the increase in diaphragm length remains constant, can there be an adaptive rightward shift of the diaphragm's force–length relationship.

Pulmonary Gas Exchange

Since at least 1901, pulmonary edema has been a known complication of uremia [61]. The radiologic signs consist of large perihilar densities that are out of proportion to the clinical signs and symptoms [28]. On gross pathologic examination, the lungs are heavy, rubbery, and with variable amounts of eosinophilic, protein-rich edema fluid. Histologic examination shows evidence of mononuclear cell alveolar infiltrates and occasional pulmonary fibrosis [28, 53]. Increased capillary permeability plays a central role in the pathogenesis of uremic pneumonitis [42, 80] and the condition usually responds to dialysis. A negative response to treatment suggests either infection or extraosseous pulmonary calcification [75]. The latter may respond to subtotal parathyroidectomy if diagnosed early [62].

A reduced carbon monoxide diffusing capacity (DLCO) is a frequent and often isolated finding in uremic patients without clinical or radiographic evidence of pulmonary disease [40, 64, 105]. In 2 of the 3 studies cited, the DLCO remained below predicted values even after correction for anemia [40, 64]. It is often impossible to ascertain whether this condition results from circulating uremic toxins, volume overload, hypoproteinemia, ventricular failure, extraosseous pulmonary calcification, vasculitis, infection, and/or immunosuppression. Renal transplantation does not appear to cause further reductions in the

DLCO and therefore a role for immunosuppressive agents in this process is unlikely [64, 105].

Hemodialysis may correct volume-overload-induced diffusion abnormalities [105] but may also induce arterial hypoxemia [8, 19, 94]. The decrease is reported to be 10–20% of the baseline oxygen tension and, thus, clinically significant hemoglobin desaturation is only expected in patients with coexistent cardiopulmonary diseases. The two major causes proposed include ventilation–perfusion mismatching from complement-mediated pulmonary leukocyte aggregation or reflex alveolar hypoventilation due to extrapulmonic (dialysate) CO_2 losses. Additional proposals include microembolization from fibrin or blood clots [8] and alterations in O_2 consumption, CO_2 production [33, 99], or oxyhemoglobin affinity [100]. This subject was superbly reviewed by Eisner [32] and by Duarte [29] in 1985, but several important studies have been published since then.

Studies using cuprophane [9, 17, 19] or cellulose [66] membranes have shown a correlation between decreases in the total WBC count, arterial PO_2, and diffusing capacity (corrected for alveolar ventilation). However, ventilation/perfusion mismatching due to either microembolization [8] or pulmonary leukocyte aggregation [20] does not appear to be an adequate explanation for hemodialysis-induced hypoxemia for 3 reasons: filters that remove clots and fibrin do not prevent hypoxemia [4]; sham dialysis with a cuprophane membrane produces leukopenia but not hypoxemia [22]; and changing the dialysate membrane from cuprophane to polyacrylonitrile prevents complement activation and resulting leukopenia but not hypoxemia [30, 56].

An alternative theory was proposed by Sherlock et al. [94] when they observed that extrapulmonic CO_2 unloading during hemodialysis produced a decrease in the respiratory quotient due to a decrease in alveolar ventilation, and in some cases a small increase in O_2 consumption [9, 32, 33, 69]. When the reduced respiratory quotient is used in the alveolar gas equation, it becomes evident that the $A–aO_2$ gradient remains unchanged and alveolar hypoventilation accounts for the observed hypoxemia [9, 27, 72, 86, 92].

Sherlock et al. and Patterson et al. have both shown a 20–25% decrease in pulmonary CO_2 excretion during acetate hemodialysis [72, 94] despite the observation by Tolchin that only 5 ml/min of gasseous CO_2 (2% of CO_2 production) is transferred by diffusion into the acetate dialysate [99]. Extrapulmonic CO_2 excretion into the hemodialysis acetate bath is largely due to the net effect of bicarbonate loss into the dialysate bath followed by metabolic regeneration (Fig. 1) and only a small amount is due to the diffusion of gaseous CO_2 [32, 71].

Numerous studies have since confirmed the correlation between alveolar hypoventilation and hypoxia during hemodialysis [9, 15, 18, 24, 27, 33, 48, 52, 55, 72, 88, 92, 99]. Furthermore, hypoventilation and hypoxia are significantly reduced if not eliminated by bubbling CO_2 directly into acetate dialysate solutions [85, 92, 93] and/or by substituting bicarbonate for acetate [9, 18, 24, 27, 48, 52, 55, 70, 81, 93, 94].

Leukocyte aggregation may still play a minor role and may accentuate the effects of alveolar hypoventilation as a cause for hemodialysis-induced hypoxe-

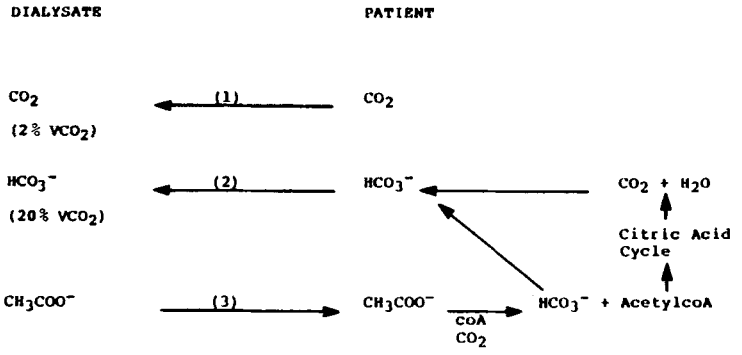

Fig. 1. Extrapulmonic carbon dioxide loss during acetate hemodialysis. Diffusion of gaseous CO_2 (1) is equal to approximately 2% of $\dot{V}CO_2$. The transfer of bicarbonate (2) is equivalent to 20% of $\dot{V}CO_2$. Acetate metabolism (3) is partially responsible for the regeneration of bicarbonate (adapted by permission from [32]).

mia. White blood cells appear to be a necessary factor because greater decreases in PaO_2 occur when patients are dialyzed against a membrane that also causes leukopenia (cuprophane and cellulose) [24] and because hypoxemia does not occur when leukopenic patients are hemodialyzed [9, 66]. Furthermore, when hypoventilation is prevented by controlled mechanical ventilation, hypoxemia may [17, 57, 58] or may not [11, 82] occur, perhaps because of dialysate membrane–blood interactions or differences in the level of acute illness present. The multiple inert gas elimination technique was used recently, to quantitate ventilation/perfusion mismatching during hemodialysis (cuprophane membrane) in mechanically ventilated dogs [82] and spontaneously breathing patients [86]. Both studies found no increase in ventilation/perfusion mismatching or $A–aO_2$ gradients and concluded that hemodialysis-induced hypoxia was primarily due to alveolar hypoventilation.

Hypoxemia may also occur during acute peritoneal dialysis. Goggins and Joekes studied 7 patients requiring acute peritoneal dialysis and found the arterial PO_2 to drop by an average of 4 mmHg after 1 L dialysate infusion and 12 mmHg after a 2 L infusion [44]. Similar changes were noted in the Aa gradient and were completely reversed by dialysate drainage. Reductions in PaO_2 during acute peritoneal dialysis are throught to result from the increase in peritoneal pressure that elevates the diaphragm, causing a decreased vital capacity, atelectasis, and increased closing volumes [41, 44]. Swartz found that the infusion of 2 L of peritoneal dialysis produced a decrease in cardiac output, an increase in pulmonary artery pressures, and diminished perfusion to both lung bases [96]. The effect may be especially pronounced during acute peritoneal dialysis when a patient's respiratory status may be already compromised by volume overload and/or infection. Hypoxemia during chronic peritoneal dialysis has not been well documented. Ahlumalia studied patients on chronic intermittent peritoneal dialysis and failed to observe a decrease in PaO_2 despite persistent

decreases in lung volumes [1]. Both Winchester and Singh failed to observe arterial hypoxemia in patients on CAPD [95, 102, 103].

Summary

Alterations in respiratory drive, mechanics, muscle function, and gas exchange are frequent if not invariable consequences of uremia. Pulmonary dysfunction may be the direct result of circulating uremic toxins or may indirectly result from volume overload, anemia, immune suppression, extraosseous calcification, malnutrition, electrolyte disorders, and/or acid–base imbalances. Acetate hemodialysis reduces alveolar ventilation and PaO_2 due to extrapulmonic CO_2 unloading. Peritoneal dialysis increases alveolar ventilation and intraperitoneal pressure. The latter leads to an elevated and lengthened diaphragm, a reduced FRC, basilar atelectasis, possible hypoxemia, and altered respiratory muscle function. In patients on CAPD, adaptations may occur that limit the reductions in lung volumes, PaO_2, and respiratory muscle strength that are often observed during acute peritoneal dialysis.

Hemodialysis and peritoneal dialysis have different physiological effects but are usually equally efficacious for the treatment of uremia. However, when moderate or severe pulmonary disease is present, the type of treatment may be just as important as the need for treatment. In patients admitted to the intensive care unit ICU for respiratory failure requiring mechanical ventilation, acute renal failure increases mortality from 20 to 80% [60, 97]. In this setting, early dialysis may improve survival [60] but peritoneal dialysis may prove superior to hemodialysis because of better hemodynamic stability. The opposite is true for patients with chronic pulmonary dysfunction and renal failure. Hemodialysis (with supplemental O_2) might be a better treatment option because acute peritoneal dialysis may precipitate respiratory failure and the need for mechanical ventilatory support. The potential effect on the respiratory system makes these treatment decisions vital, interesting, and challenging.

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