Pulmonary Gas Exchange During Hemodialysis: A Comparison of Subjects with and without COPD on Bicarbonate Hemodialysis

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Abstract. Little is known about the effect of hemodialysis (HD) on gas exchange in subjects with chronic obstructive pulmonary disease (COPD). The purpose of this study was to examine blood gases and pH in COPD patients undergoing HD with bicarbonate dialysate. We studied thirteen subjects with COPD and thirteen controls (CON). All were dialyzed for 4 hrs against a bicarbonate HD solution. Blood gases, pH and HCO_3^- were initially analyzed (t_0) and, during HD, at 30 min ($t_{0.5}$), 1 hr (t_1) and 4 hrs (t_4). At t_0 , a statistically significant difference was observed for PO_2 (CON: 84.7 ± 3.60 , COPD: 72.19 ± 4.92 ; $p < 0.001$). For the first hr, PO_2 decreased, and at t_1 , oxygen was required for 6 COPD subjects. By t_4 , there was no significant difference in PO_2 between groups. The alveolar-arterial gradient ($\Delta A-a$) remained different between groups ($P < 0.001$, all times), with increasing $\Delta A-a$ for both groups up to t_1 and decreasing over the remaining 3 hr. For both groups, at t_4 , $\Delta A-a$ was higher than at t_0 ($p < 0.001$). For PCO_2 , both groups demonstrated increases from t_0 to t_1 ($p = 0.0004$), with COPD having PCO_2 higher than CON at $t_{0.5}$ and t_1 ($p < 0.05$ for both); by t_4 , PCO_2 levels decreased to nearly the same as at t_0 . Over the 4 hr treatment, HCO_3^- and pH increased significantly for both groups; however no significant difference was observed between COPD and CON. Markedly increased $\Delta A-a$ is observed during HD in some COPD patients. COPD patients retain more CO_2 . However, the effect of HCO_3^- leads to mild metabolic alkalosis at t_4 .

Key words: Bicarbonate hemodialysis; acid-base equilibrium; chronic obstructive pulmonary disease; pulmonary gas exchange; blood gases.

Introduction

Hypoxemia during hemodialysis (HD) is a well-described phenomenon [1-5]. Although several mechanisms have been proposed [6], the cause remains unclear. Some studies have attributed hypoxemia during HD to the type of dialysate [7], to the type of membrane used [8], or to both [9-11]. Acetate dialysate, for example, has been found to trigger hypoxemia by the loss of carbon dioxide (CO_2) across the dialyzer [12,13]. This loss in CO_2 results in alveolar hypoventilation. Ventilation/perfusion (V/Q) mismatch has been proposed as the cause of hypoxemia by Craddock *et al.* [14] and

Bischel *et al.* [15]. It has also been suggested that the activation of the complement system by the non-biocompatible dialysis membrane triggers pulmonary leukostasis [14].

As the cause of hypoxemia during HD remains under debate, the effects of this repetitive transient hypoxemia on chronic obstructive pulmonary disease (COPD) patients should also be considered. As this minor degree of hypoxemia may remain tolerable in normal subjects, patients with pulmonary compromise may not be able to tolerate it over an extended period of treatment. In fact, this hypoxemia may well contribute to these patients' morbidity and even mortality.

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Therefore, we have elected to study the effects of bicarbonate-based HD on gas exchange in patients with COPD and to compare them to the effects on subjects without COPD. The purpose of our study is to examine the abnormalities of gas exchange that take place in COPD patients.

Materials and Methods

Patients and Protocol. A cohort consisting of twenty-six HD patients was divided into two groups: those with a diagnosis of COPD, based on the criteria of the Global Initiative for Chronic Obstructive Lung Disease for all classes of COPD, i.e., $FEV_1/FVC < 70$ [16], and a control group that had no clinical evidence of COPD. Of 265 subjects screened for inclusion, 13 were determined to have COPD; the age and sex-matched controls were sequentially chosen from the remaining subjects without COPD. In each group, there were 8 males and 5 females. All of the 13 patients with COPD were smokers while 4 of the 13 controls were non-smokers. The patients were included in the study if they were over 21 years of age, underwent dialysis via established arteriovenous (A-V) fistulae, and were on dialysis for more than 6 months. Patients were excluded if they did not meet all the inclusion criteria, or if they had chronic respiratory failure requiring the use of continuous or intermittent oxygen therapy, or had a baseline resting PO_2 of less than 60 mmHg on room air. Because patients were required to have been on maintenance dialysis for a minimum of six months, fistulae were considered to be fully arterialized.

This observational study examined changes in PO_2 , PCO_2 , pH, and HCO_3^- and the alveolar-arterial oxygen gradient, $\Delta A-a$. Arterial blood was drawn from the A-V fistula for the first specimen immediately before the initiation of HD. The second and third specimens were drawn from the A-V fistula at 30 and 60 min, respectively, after the initiation of HD. The fourth specimen was drawn at 240 min, immediately before the termination of HD.

The study was approved by Institutional Review Board at St. Joseph's Regional Medical Center.

O₂ Supplementation. In cases where blood PO_2 was found to drop significantly during or after HD, the patients were provided with supplemental O_2 according to the following algorithm: For COPD patients: the supplementation threshold was a $PO_2 \leq 60$ mmHg; for an individual without known underlying lung disease, a

$PO_2 < 70$ mmHg was considered the threshold for O_2 supplementation. Supplementation with O_2 was done via nasal cannula.

Dialysis Procedure. Therapy sessions with HD were performed using Fresenius K machines. All the subjects were dialyzed with a bicarbonate dialysate bath (HCO_3^- concentration at our standard protocol of 37 mEq per liter) in which the acetate concentration was 4 mEq/l. The dialyzers were Fresenius Optiflux using new polysulfone membranes. AV fistulas were used for cannulation with either 14 or 15 gauge needles. Blood flow was maintained at 300–400 ml/min.

Patients were studied for two dialysis sessions; the mean of the two values for each patient were used. The session to session values never varied by more than ten percent.

Blood Gas Analysis. Blood samples, taken from the A-V fistula within 6 cm of the anastomotic site to minimize venous mixing, were drawn into syringes that were immediately capped and placed on an ice bath. The PO_2 , PCO_2 , pH, and HCO_3^- were analyzed on a Gem® Premier 2000 Blood Gas Analyzer (Instrumentation Laboratory (Lexington MA, USA) 5–10 minutes after being drawn. All analyses were within acceptable analytical standards for the instrument controls. The $\Delta A-a$ was calculated as the difference between the alveolar PO_2 and arterial PO_2 , with alveolar O_2 concentration calculated from the formula: $P_{AO_2} = [\text{Fractional concentration of inhaled oxygen} \times (\text{barometric pressure} - \text{partial pressure of water vapor in air})] - P_{aCO_2}/0.8$.

Statistical Analysis. For this study, α was set at 0.05; comparisons for which $p < 0.05$ (two-sided) were considered to demonstrate significant differences between groups. Categorical variables were compared using cross-tabulations and analyzed for statistical significance by Fisher's exact test. Continuous variables were tested for fit-to-normality with the D'Agostino–Pearson omnibus normality test. Because all but three groups (PO_2 , 30 min. COPD group, PO_2 , 240 min. Control group, and $\Delta A-a$, initial, COPD group) were normally distributed, parametric methods were used, with data expressed throughout as means $\pm$ 1 standard deviation (SD). A two-way ANOVA model for each dependent variable (PO_2 , $\Delta A-a$, PCO_2 , pH, and HCO_3^-) considered two independent variables: (1) group as an independently assorted measure and (2) time, as a repeated measure.

Data were analyzed using Prism® software (GraphPad Corp., San Diego CA, USA) on a personal computer–Windows® Vista® platform.

Table 1. Baseline characteristics of the study groups. Categorical variables other than gender are presented as those with/ those without the indicated condition.

Characteristic	COPD	No COPD	p-value
Age, yrs (mean $\pm$ SD)	63.1 $\pm$ 10.4	61.2 $\pm$ 15.4	0.724
Gender (M/F)	8/5	8/5	1.00
BMI (mean $\pm$ SD)	24.7 $\pm$ 3.78	22.3 $\pm$ 3.46	0.151
Hypertension	10/3	8/5	0.673
Diabetes	5/8	7/6	0.695
Dyslipidemia	4/9	6/7	0.688
Coronary artery disease	2/11	4/9	0.645
Cardiomyopathy	3/10	1/12	0.593
Peripheral vascular disease	1/12	3/10	0.593
Systemic lupus erythematosus	0/13	1/12	1.00
Rheumatoid arthritis	0/13	1/12	1.00
Hepatitis B	1/12	0/13	1.00
Hepatitis C	1/12	1/12	1.00
HIV disease	0/13	1/12	1.00

Results

Baseline demographics for the two groups are provided in **Table 1**. There were no significant differences with regard to either basic demographics or co-morbidities.

Parameters relating to oxygenation are shown in **Figure 1**. The COPD group demonstrated significantly ($p < 0.0001$) lower initial PO_2 and this trend continued over the course of the first hour of dialysis (change over time also statistically significant at $p < 0.0001$). The apparent increase in PO_2 for the COPD subjects is due to their having received O_2 supplementation, as described in METHODS. In fact, as can be seen in the plot of $\Delta A-a$, the differences in that parameter trended ($p < 0.0001$) in the same direction with a comparably significant difference ($p < 0.0001$) between the groups.

Figure 2 provides data on PCO_2 , HCO_3^- and pH. Not unexpectedly, initial PCO_2 in the COPD group is elevated and remains significantly so ($p < 0.0001$) over the first hour of HD. By 4 hr, the PCO_2 diminishes to a value close to the control group; in fact, there was no significant difference observed between the two groups by that time.

A slightly significant difference in HCO_3^- is seen during the course of the HD treatment overall ($p = 0.026$), although post-tests failed to detect

a difference at any single time period. The time factor was highly significant ($p < 0.0001$) as plasma HCO_3^- reached equilibrium with the HCO_3^- concentration of the bath.

For pH, although a significant difference ($p = 0.004$) is observed between the groups, only the difference at 1 hr was detected as significant by post-test. Initially the COPD and control pH values are quite comparable; however, over the course of the HD treatment both groups trend toward a metabolic alkalosis. This is alleviated, to a degree, in the COPD group, whose PCO_2 values increase to demonstrate partial respiratory compensation.

Discussion

This study demonstrates that hypoxemia during HD occurs in both patients with and without COPD to nearly the same degree. However, due to the fact that patients with COPD have a lower baseline PO_2 , the nadir PO_2 in this group was lower. The comparable values of PO_2 that were seen at the end of HD were due to O_2 supplementation to patients with COPD whose PO_2 fell below 60 mmHg during the first hour of the HD session. While Serrano *et al.* showed that the occurrence of hypoxemia during the first hour of HD only in subjects with chronic pulmonary disease

Figure 1. Parameters of blood oxygenation over the course of a four-hour HD treatment. Data are means $\pm$ 1 SD

undergoing bicarbonate HD [17], Pitcher *et al.* demonstrated the occurrence of hypoxemia only at the end of the HD session in subjects with and without COPD [18]. In contrast, our study showed that hypoxemia during bicarbonate HD occurred at 30 minutes, peaked at 60 minutes and continued until the end of the HD session. The cause of this hypoxemia during the first hour of HD is unclear. The minute ventilation during bicarbonate HD was found to be decreased in the control group during the first hour of HD but not to a point reaching statistical significance [18]. Therefore, bicarbonate-induced hypoventilation may be one mechanism that could explain hypoxemia within the first hour of HD. Other proposed theories are V/Q mismatch, activation of complement, and microembolization to the lungs [6]. However, these mechanisms do not explain the persistence of hypoxemia throughout the HD session. Moreover, the use of a polysulfone membrane minimizes the activation of complement and pulmonary leukostasis, thereby minimizing their contribution to the observed degree of hypoxemia [8].

Our data also demonstrate a comparable rise in PCO₂ in both COPD and non-COPD subjects. However, because the baseline PCO₂ in subjects

with COPD is higher than in the control subjects, the nadir PCO₂ in subjects with COPD remains higher. These findings are consistent with a previously observed rise in PCO₂ during HD [18]. The rise in PCO₂ could be explained theoretically by both hypoventilation and V/Q mismatch. The most likely cause of the decline in PCO₂ towards the end of dialysis is the resolution of hypoventilation induced by hypoxemia.

We observed comparable changes in HCO₃⁻ in both COPD and non-COPD. Ultimately both groups' plasma HCO₃⁻ levels equilibrate to the concentration in the dialysate. A continuous rise in pH was observed in both the COPD and the control groups. This rise in pH mirrors the rise in serum bicarbonate in both groups.

In summary this study is the first prospective study done on COPD patients undergoing bicarbonate HD to observe the effect of HD on all arterial blood gas components including: PO₂, ΔA-a, PCO₂, HCO₃⁻ and pH. Our data clearly show that hypoxemia during bicarbonate HD takes place within 30 minutes of initiation of HD and peaks at 60 minutes in *both* COPD and non-COPD subjects. To our knowledge this has not been previously demonstrated. Serrano *et al.* demonstrated hypoxemia at 30 and 60 minutes in the chronic lung disease group only and failed to detect any hypoxemia in the control group at the aforementioned intervals [17]. Pitcher *et al.* did not demonstrate any hypoxemia in either the control or the COPD groups at one-hour post initiation of HD [18]. In contrast, our study showed that hypoxemia occurs within the first hour and continues throughout the HD session.

The fact that hypoxemia continues throughout the HD session leaving the COPD subjects with a higher ΔA-a at the end of the session than at the initiation of the HD session shows the necessity of supplementing these patients with oxygen during and after HD. In fact, oxygen supplementation in these patients may eliminate the consequences of repetitive hypoxemia such as arrhythmias and acceleration of the development of pulmonary hypertension. Moreover, our data, when examined in light of data on other membrane and buffer systems, suggest that there may be cause to examine HD patients more routinely for V/Q mismatch as evidenced by increased A-a gradients.

Figure 2. Acid-base parameters (PCO_2 , HCO_3^- , and pH) during HD. Data expressed as in the previous figure.

Alkalosis is another factor that may contribute to morbidity and mortality in patients on HD. In our study a significant degree of alkalosis was observed among patients, especially at the end of HD session, as a considerable number of subjects had a pH above 7.5, the result of using the bicarbonate dialysate. The effects of this alkalosis on these patients and methods of eliminating it certainly bear further investigation. Recent data suggest that there may be higher incidence of deaths on Mondays and Tuesdays after the two-day gap in HD treatments. Although it is purely hypothetical, it is tempting to speculate that this increased mortality may be related to the initial acidosis and rapid correction of pH to the alkalotic side with concomitant electrolyte shift and arrhythmias [191]. This also needs to be further explored, especially in that arterial blood

is easily accessed in this group of subjects obviating the need for direct arterial puncture.

We recognize that our study has some limitations. We studied only thirteen subjects in each group. This is unlikely to have been problematic in terms of the primary dependent variables, as the within-group dispersion for each variable (**Figures 1 and 2**) can be observed to be relatively small. However the baseline characteristics (**Table 1**) include several comparisons for which statistical analysis suggests that there is no difference between groups when, in fact, this may represent a Type 2 testing error, i.e., we may not have had adequate power to detect a difference.

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References

1. Habte B, Carter R, Shamebo M, Veicht J, Boulton Jones JM. Dialysis Induced Hypoxemia. *Clinical Nephrology*. 1982 Sep; 18(3): 120-125.
2. Kishimoto T, Tanaka H, Maekawa M, Ivanovich P, Levin N, Bergstrom J, Klinkmann H. Dialysis-Induced Hypoxemia. *Nephrol Dial Transplant*. 1993; 8 [Suppl. 2]: 25-29.
3. De Broe ME. Hemodialysis-Induced Hypoxemia. *Nephrol Dial Transplant*. 1994; 9 [Suppl. 2]: 173-175.
4. Fawcett S, Hoenich NA, Laker MF, Schorr Jr W, Ward, MK, Kerr DNS. Hemodialysis-Induced Respiratory Changes. *Nephrol Dial Transplant* 1987; 2: 161-168.
5. Garella S, Chang BS. Hemodialysis-Associated Hypoxemia. *Am. J. Nephrol* 1984; 4: 273-279.
6. De Broe ME, Heyrman, RM, De Backer WA, Verpooten GA, Vermeire PA. Pathogenesis of Dialysis-Induced Hypoxemia: A Short Overview. *Kidney International*, 1988; 33(24): S57-S61.
7. Abu-Hamdan DK, Desai SG, Mahajan SK, Muller BF, Briggs WA, Lynne-Davies P, McDonald FD. Hypoxemia during hemodialysis using acetate versus bicarbonate dialysate. *Am. J. Nephrol*. 1984; 4: 248-253.
8. Jacob AI, Gavellas G, Zarco R, Perez G, Bourgiogonie JJ. Leukopenia, hypoxia and complement function with different hemodialysis membranes. *Kidney International* 1980; 18: 505-509.
9. Francos GC, Besarab A, Burke J, Peters J, Tahamont MV, Gee MH, Flynn JT, Gzesh D. Dialysis-Induced Hypoxemia: Membrane Dependent and Membrane Independent Causes. *American Journal of Kidney Diseases*, 1985 March; V(3): 191-198.
10. De Backer W, Verpooten GA, Borgonjon Dj, Vermeire PA, Lins RR, De Broe ME. Hypoxemia during hemodialysis: Effects of different membranes and dialysate compositions. *Kidney International* 1983; 23: 738-743.
11. Igarashi H, Kioi S, Gejyo F, Arakawa M. Physiologic Approach to Dialysis-Induced Hypoxemia: Effects of Dialyzer Material and Dialysate Composition. *Nephron*. 1985; 41: 62-69.

12. Dumler F, Levin NW. Leukopenia and Hypoxemia. *Arch Intern Med* 1979 Oct; 139: 1103-1106.
13. Aurigemma NM, Feldman NT, Gottlieb M, Ingram RH JR, Lazarus JM, Lowrie EG. Arterial Oxygenation During Hemodialysis. *N Engl J MED*. 1977; 297: 871-973.
14. Craddock PR, Fehr J, Dalmaso AP, Brigham KL, Jacob HS. Hemodialysis Leukopenia: Pulmonary Vascular Leukostasis Resulting from Complement Activation by Dialyzer Cellophane Membranes. *The Journal of Clinical Investigation* 1977 May; 59: 879-888.
15. Bischel MD, Scoles BG, Mohler JG. Evidence for Pulmonary Microembolization during Hemodialysis. *Chest* 1975; 67: 335-337.
16. Global Initiative for Chronic Obstructive Lung Disease. A collaborative project of the National Heart Lung and Blood Institute, NIH (USA) and the World Health Organization. Global Initiative for Chronic Obstructive Lung Disease, 2006. <http://www.goldcopd.com> (last accessed Aug. 9, 2011).
17. Serrano RP, Vega FF, Grande JA. Hypoxemia during hemodialysis in patients with impairment in pulmonary function. *Nephron* 1986; 42: 14-18.
18. Pitcher WD, Diamond SM, Henrich WL. Pulmonary Gas exchange during dialysis in patients with obstructive lung disease. *Chest* 1989; 96: 1136-1141.
19. TR Davis, BA Young, MS Eisenberg, TD Rea, MK Copass, LA Cobb. Outcome of cardiac arrests attended by emergency medical services staff at community outpatient dialysis centers. *Kidney International* 2008; 73: 933-939.