

# Branched-chain amino acid in chronic renal failure patients: Respiratory and sleep effects

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**Branched-chain amino acid in chronic renal failure patients: Respiratory and sleep effects.** Sleep disorders, including a high incidence of sleep apnea, have been recognized as a significant problem in chronic renal failure (CRF) patients. In a preliminary study, we examined CRF patients on maintenance hemodialysis for three nights; one control night, and thereafter randomized to infusion of saline (placebo) for one night and 4% branch-chain amino acid (BCAA) solution for one night. Polysomnographic and respiratory data [respiratory rate, oxygen saturation and end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>)] was recorded continuously throughout the nights and data from each hour compared with baseline (awake) values. The patients studied were characterized by reduced sleep quality and decreased amount of rapid eye movement (REM) sleep. The BCAA infusion was associated with a return of REM sleep to normal and a significant decrease in ETCO<sub>2</sub> during both REM and non-REM sleep ( $P < 0.05$ ). Our findings demonstrate respiratory stimulation during sleep with infusion of BCAA; this stimulatory effect on respiration (in contrast to many respiratory stimulants) is associated with an increased amount of REM sleep.

Sleep disorders have become a topic of increasing clinical interest in chronic renal failure (CRF) patients on hemodialysis (HD) [1–3]. The sleep disorder may take the form of an abnormal pattern of sleep and increased requirements for medication as well as an overt sleep apnea. Both obstructive apnea (no airflow but respiratory effort) and central apnea (no airflow and no respiratory effort) occur in CRF patients [2, 4]. The detrimental clinical effects of sleep apnea include arterial oxygen desaturation, cardiac arrhythmias, and pulmonary and systemic hypertension [5]. Although the effects of an abnormal pattern of sleep are less clinically severe, nonetheless these patients frequently report daytime drowsiness and fatigue which limit functional capacity. Mood and personality disorders as well as impaired intellectual functioning may also be observed [6, 7]. Conventional hemodialysis has not been found to modulate the severity of sleep apnea [3]. Significant improvements in both physiology and symptomatology have been reported with different pharmacological agents such as theophyllamin, acetazolamid, and protriptyline [6–10]. However, potential side effects (peripheral neuropathy, paresthesia, aci-

dosis, impotence, and dry mouth) and changes in sleep quality have limited the use of these agents [6, 9, 10].

Takala et al [11] demonstrated that infusion of branch-chain amino acid (BCAA) enriched solutions magnify the increase in ventilatory chemosensitivity to CO<sub>2</sub> observed with regular amino acid solutions [12, 13]. As a consequence, the minute ventilation increased significantly, and a significantly decreased arterial PaCO<sub>2</sub> was observed as well. In a previous study [14] of normal subjects we found that nocturnally infused BCAA was associated with no changes in sleep quality but with a significantly decreased end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>). This observation was probably due to improved alveolar gas exchange [11]. Intravenous BCAA administration is considered to be without toxic side effects, and BCAA may therefore be an useful alternative as respiratory stimulant in treatment of sleep apnea.

With this background, we found it of interest to study the effects of nocturnally infused BCAA on respiratory patterns and sleep in a group of CRF patients undergoing maintenance hemodialysis (HD). This study could then act as a basis for further investigations of the role of intradialytic BCAA administration in CRF patients with sleep disorders.

## Methods

### Patients

Patients were selected from the Baumritter Kidney Center's in-center hemodialysis population. A standard questionnaire was administered to all patients. Those patients who reported remarkable sleep disturbances (several awakenings during the night, difficulties in falling asleep, daily drowsiness, etc.) were considered for the study. Written informed consent was obtained from all subjects, and the study was approved by the Institutional Review Board of The Albert Einstein College of Medicine at Montefiore Medical Center.

Seven CRF patients (3 female and 4 male) treated with HD three times a week agreed to undergo nocturnal polysomnography and were studied on three nights prior to HD on the following day. None of the patients had concomitant liver, heart or lung diseases. Patients were dialyzed according the kinetic modeling principles developed by Gotch and Sargent [15], and achieved kinetic modeling parameters (KT/V) of 1.0 or greater, which is accepted as an indicator of adequate dialysis. Patients treated with sedatives or antihistamines had to discontinue

**Table 1.** Arterial blood gas values and sleep pattern (N = 6)

|                        | Study patients | Normal values |
|------------------------|----------------|---------------|
| Arterial blood gases   |                |               |
| pH                     | 7.41 ± 0.08    |               |
| PCO <sub>2</sub> mm Hg | 40.4 ± 3.0     |               |
| PO <sub>2</sub> mm Hg  | 93.4 ± 4.5     |               |
| Base excess mmolliter  | 3.1 ± 5.7      |               |
| Sleep pattern          |                |               |
| Stages 1 and 2 %       | 66 ± 12        | 63 ± 9        |
| Stages 3 and 4 %       | 19 ± 9         | 12 ± 6        |
| REM sleep %            | 14 ± 8         | 23 ± 4        |
| Sleep efficiency %     | 70 ± 12        | 97 ± 2        |
| Sleep latency min      | 21 ± 15        | 6 ± 4         |

Data are presented as mean ± SD. Normal values are based on international standards applied by sleep laboratories, matched with age and sex. Definitions are: sleep efficiency = total sleep time divided with total recording time; sleep latency = the interval between lights out and sleep onset.

them during the study period. Six of the patients were on antihypertensive medications, including beta blockers. The polysomnographic investigation revealed that only one patient had severe sleep apnea. This patient was very different from the rest both with respect to sleep and respiratory pattern, and he is therefore presented separately. The mean age of the six patients without apnea was 43 years (range 36 to 48 years). Their mean dry weight given as the percent of ideal body weight (The Revised Metropolitan Ideal Body Weight Tables, 1985) was 91% (range 76 to 110%). Table 1 shows patient characteristics of the six non-apneic patients.

#### Procedure

No food intake was allowed after 5 p.m. on any of the three study nights. On infusion nights, a peripheral line (22G) was inserted in the arm contralateral to the arterio-venous dialysis access. The patients did not receive any infusion the first night (control). They were subsequently randomized, in double-blind, cross over fashion, to receive either BCAA (60 mg/kg/hr = 1.4 ml/kg/hr, corresponding to 100 ml/hr in a 70 kg person) or saline, intravenously, for seven hours on the two study nights. The infusions were started one hour before habitual bedtime. The BCAA solution (4% Branchamin-Baxter) contained 1.38 g of isoleucine and leucine each per 100 ml, and 1.24 g of valine per 100 ml.

Surface electrodes and a 12 channel Grass P78 polysomnograph (PSG) were employed for continuous recording of the electroencephalogram, submental electromyogram, electrooculogram, and electrocardiogram [4, 16]. Respiratory movements were monitored with pneumograph bellows around the chest and abdomen and recorded on the PSG [4]. The pneumograph bellows were used in a semiquantitative fashion to allow differentiation of obstructive and central apneas and hypopneas.

A finger oximeter (Ohmeda Biox 3700, Ohmeda, Louisville, Colorado, USA) with an accuracy of ±1.5% and a capnograph (Normocap, Datex, Helsinki, Finland) with an accuracy of ±2% were used to record oxyhemoglobin saturation (SaO<sub>2</sub>) and ET<sub>CO</sub><sub>2</sub> [4, 17]. To measure ET<sub>CO</sub><sub>2</sub> a length of thin tubing was inserted about 1 cm into the nostril and the other end connected to the sample port of a capnograph [4, 18]. The capnograph was

calibrated prior to each night's study. Both the oximeter and capnograph were connected to the PSG for continuous recording. The presence of airflow was inferred by the ET<sub>CO</sub><sub>2</sub> and by thermocouples at the nose and mouth.

#### Data analysis

The polysomnograms were scored for sleep stages and incidence, length and severity of apneas/hypopneas by a registered polysomnographic technologist unfamiliar with the premises of the study. Following the traditional staging and scoring definitions introduced originally by Rechtschaffen and Kales [19], sleep was divided into REM (rapid eye movement) sleep and non-REM sleep (Stages I to IV) [4, 16]. Stages I and II comprise light sleep, whereas stages III and IV constitute slow or delta wave sleep. Sleep progresses through these stages to REM sleep. In this paper, sleep stages and REM sleep are expressed as percentages of total sleep time.

Obstructive apnea was defined as the absence of airflow in the presence of rib cage and abdominal excursions for a period of at least 10 seconds, while non-obstructive (central) apnea was defined as the absence of both airflow and respiratory movement for at least 10 seconds [2, 4, 6]. Apneas with both obstructive and central characteristics ("mixed") were classified together with the obstructive apneas [4]. Hypopnea was defined as an episode of at least 10 seconds in which the amplitude of the sum of ventilatory movement of rib cage and abdomen was less than 50% of the mean amplitude of the previous breaths. Five or more apneas per hour of sleep was considered abnormal and apnea associated with more than 5% desaturation was considered severe.

Analysis of ET<sub>CO</sub><sub>2</sub>, SaO<sub>2</sub>, and respiratory and heart rate was carried out during blocks of three to five minutes of stable breathing (no apneas) in every sleep stage that was recorded during each hour of the sleep study. Only CO<sub>2</sub> polygraph waveforms consisting of a sharp upstroke and downstroke with a relatively flat plateau which had a slightly ascending slope were considered valid for analysis of ET<sub>CO</sub><sub>2</sub> [4, 18, 20]. During each hour, the block selected for analysis was as close as possible to the middle of the hour. Thus, the measurements of breaths during each hour of sleep avoided potential bias associated with selecting breaths from only one point in time during the night of polysomnography [21]. The baseline consisted of a five minute block of stable breathing after the patient retired and before onset of sleep. Mean values were obtained by averaging all measurements over the three to five minute periods. Data from baseline were compared to hourly measurements from midnight to 5 a.m. This particular period was chosen since some patients did not fall asleep until midnight and many of them had to get up at 5 a.m. for early dialysis. The data from non-REM periods analyzed were for stages 1 and 2 because adequate data for stages 3 and 4 were missing in many patients. The patients had infrequent periods of REM sleep, which usually occurred at the end of the study period. Therefore, data from the last recorded REM period was used for comparison with baseline and non-REM values.

Statistical analysis was performed using SYSTAT software (Evanston, Illinois, USA). A repeated measures model was used (MANOVA) to control for possible individual differences and to compare the three measurement periods. Post-hoc comparisons were made by the Tukey test. When applicable,

**Table 2.** Polysomnographic and respiratory data ( $N = 6$ )

|   | Saline  | BCAA    | <i>P</i> value |
|---|---------|---------|----------------|
| Stage 1 %                               | 9 ± 3   | 6 ± 3   | NS             |
| Stage 2 %                               | 56 ± 19 | 53 ± 10 | NS             |
| Stages 3 and 4 %                        | 21 ± 14 | 20 ± 11 | NS             |
| REM sleep %                             | 12 ± 10 | 19 ± 8  | <0.05          |
| Sleep efficiency %                      | 66 ± 16 | 74 ± 13 | NS             |
| Sleep latency min                       | 39 ± 35 | 12 ± 10 | = 0.11         |
| Arousals total                          | 30 ± 12 | 35 ± 14 | NS             |
| Arousals >5 min                         | 5 ± 3   | 5 ± 2   | NS             |
| Apnea index number/hr of sleep          | 2 ± 2   | 2 ± 3   | NS             |
| Apnea-hypopnea index number/hr of sleep | 3 ± 4   | 4 ± 5   | NS             |
| Baseline SaO <sub>2</sub> %             | 97 ± 2  | 96 ± 1  | NS             |
| Lowest SaO <sub>2</sub> %               | 90 ± 3  | 88 ± 5  | NS             |

Data are presented as means ± SD.

for paired data the Student's *t*-test was performed. A *P* value less than 0.05 was considered statistically different.

### Results

Seven patients completed the three night study. Compared to values for their age-matched normal subjects (based on the international standards applied by sleep laboratories) the six patients without sleep apnea were characterized by both less REM sleep and reduced sleep quality, as evidenced by prolongation in time to fall asleep and reduced time spent in sleep during the night as compared with normal reference values (Table 1). When sleep and respiratory data from the night of BCAA and saline infusion was compared, a significant increase in REM sleep ( $P < 0.05$ ) was found with BCAA (Table 2). A reduction in time to fall asleep with BCAA was observed, but the difference did not reach statistical significance.

Baseline ET<sub>CO</sub><sub>2</sub> for each night was compared with values for each hour throughout the night. On the placebo (saline) night no changes in ET<sub>CO</sub><sub>2</sub> could be measured. With BCAA, however, there was a significant decrease (11%) in mean ET<sub>CO</sub><sub>2</sub> during the seven hours of infusion both for non-REM ( $P < 0.05$ ) and REM sleep ( $P < 0.05$ ; Fig. 1). Respiratory rate (ranging in means between 16 to 19 breaths/min) and SaO<sub>2</sub> (in mean range of 94.5% to 96%) did not change significantly from baseline throughout the study nights, nor were there any significant changes in heart rate.

Patient #7 (Table 3) had severe sleep apnea and also differed from the other patients in that he was overweight (150% of ideal body weight). The patient had markedly reduced sleep efficiency on both nights (Table 3). Due to continuous arousals in connection with the apneas his sleep was scored as transitional sleep, type non-REM and REM [4, 19]. There was no significant increase in the ratio of REM to non-REM sleep when comparing the night of saline and BCAA (Table 3). However, the BCAA night in this patient was associated with a large decrease in the total number of obstructive apneas, corresponding to a fall in the apnea index from 85 to 31. Furthermore, no central apneas occurred that night, and the mean duration of both obstructive apneas and hypopneas was lowered with BCAA (30 vs. 26 sec, and 30 vs. 20 sec, respectively). These changes were also associated with improvements in oxygen saturation. While the apneas on the saline night were associated with regular

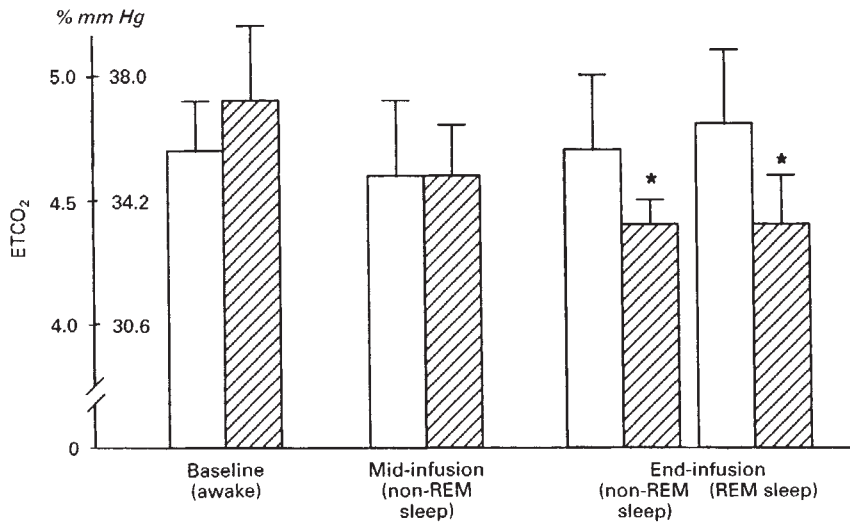
desaturations from a baseline of 95% decreasing to about 40%, the hypopneas and majority of the apneas seen on the BCAA night only caused desaturation down to around 70%. On both nights the apnea induced desaturation was worse during REM sleep. Despite improvements with BCAA, the severity of his sleep apnea made this patient a candidate for trial of nocturnal Continuous Positive Airway Pressure (CPAP) mask [4, 6], and he was referred for this.

### Discussion

Abnormalities of sleep pattern with reduced sleep quality are common in CRF patients on HD. However, few studies have been undertaken to look at pathogenesis and treatment of sleep disturbances in these patients [22]. When compared to age-matched values for normal range, our patients showed poorer sleep quality (less time spent in sleep, increased time to fall asleep and less REM sleep). Further, the larger standard deviations of sleep parameters compared to the values for normal subjects indicated markedly larger interindividual variations. Although this study was designed to observe potential changes in ventilation, the unexpected finding of an improvement in REM sleep was observed. The infusion of BCAA significantly increased the percentage of REM sleep in our patients. It also tended to reduce the time before falling asleep (sleep latency) but did not improve actual time spent in sleep (sleep efficiency). No changes in the non-REM sleep stages were found.

In our study the infusion of BCAA appeared to stimulate respiration. The decrease in ET<sub>CO</sub><sub>2</sub> found with BCAA in our study is in agreement with previous studies of both awake and asleep normal subjects [11, 14]. The use of ET<sub>CO</sub><sub>2</sub> to monitor ventilation during sleep studies is well established [4, 18]. Göthe et al [18] showed that in normal subjects sleep was associated with decreased ventilation and a rise in ET<sub>CO</sub><sub>2</sub>. Kirvelä et al [14] also interpreted the decrease in ET<sub>CO</sub><sub>2</sub> with BCAA as a sign of improved ventilation during sleep. Takala et al [11], however, measured changes in PaCO<sub>2</sub> and ventilatory response to CO<sub>2</sub> inhalation during BCAA infusion and correlated this to minute ventilation, tidal volumes and metabolic rate. We measured ET<sub>CO</sub><sub>2</sub> and assumed that in these fasting and resting subjects the only change in CO<sub>2</sub> production would be due to BCAA infusion. Therefore, the changes in ET<sub>CO</sub><sub>2</sub> would correspond to changes in respiratory drive to a similar degree as in the study of Takala et al [11]. In patients without pathological dead-space ventilation, ET<sub>CO</sub><sub>2</sub> corresponds well with alveolar CO<sub>2</sub>, and hence PaCO<sub>2</sub>, as long as only normal capnographic waveforms are analyzed [4, 20]. None of our patients had symptomatic lung disease. We therefore believe the decrease in ET<sub>CO</sub><sub>2</sub> during BCAA infusion in our patients can be taken as a sign of increased respiratory drive and improved alveolar ventilation [11, 18]. The infusion rate of BCAA in the present study was the same as in the study of awake normals [11], but we used 100% instead of 85% BCAA solution. Unlike the study in awake normals [11], we did not observe any significant increase in respiratory rate with BCAA.

Kimmel, Miller and Mendelsohn [2] found that the incidence of sleep apnea in CRF patients was close to 10%. They further showed that in approximately half of the patients, sleep apneas were primarily of the obstructive type. In the rest, more than half of the apneas and hypopneas were of central origin. In the



**Fig. 1.** End-tidal CO<sub>2</sub> during nocturnal infusion of saline (□) and of 4% BCAA (▨) solution (mean ± SE). There was significant decrease in mean ETCO<sub>2</sub> during the BCAA infusion both for non-REM and REM sleep ( $P \leq 0.05$ ).

**Table 3.** Sleep and respiratory data for Patient #7 (male, 38 years old) with severe obstructive sleep apnea

| Night                           | Saline | BCAA |
|---------------------------------|--------|------|
| Transitional sleep <sup>a</sup> |        |      |
| non-REM                         | 62%    | 57%  |
| REM                             | 23%    | 17%  |
| Arousals                        | 15%    | 24%  |
| Sleep efficiency %              | 55%    | 47%  |
| Total number apnea              | 323    | 94   |
| Obstructive                     | 319    | 94   |
| Central                         | 4      | 0    |
| Apnea index                     | 85     | 31   |
| Total number hypopneas          | 190    | 395  |
| Apnea/hypopnea index            | 135    | 160  |
| Oxygen saturation %             |        |      |
| Baseline                        | 94     | 96   |
| Lowest                          | 34     | 54   |

Transitional sleep <sup>a</sup> Sleep continuously interrupted by arousals [4]

one patient with severe obstructive sleep apnea in our study group, BCAA reduced both the total number of apneas and the severity of oxygen desaturation in the remaining apneas and hypopneas. The oximeter used in our study has previously been tested for accuracy down to oxygen saturation levels of 40% and found reliable within 2 to 3% [17]. Therefore, we believe that observed differences in oxygen saturation are authentic and not due to technical errors. Although the beneficial response seen in this patient is only preliminary and may have been influenced by other factors, such as physiological night-to-night variability in the severity of sleep apnea, this case report may still be of importance in that it indicates the necessity for further studies about the usefulness of BCAA in the treatment of sleep apnea in CRF patients.

At present, the use of respiratory stimulants in sleep apnea is controversial [5, 6, 10]. Besides the high incidence of toxic side-effects, the main critique of pharmacological interventions in sleep apnea has been concurrent worsening of sleep quality [6, 9, 23]. In CRF patients the majority of sleep apneas occur in non-REM sleep stages I and II [2]. Previously, the use of respiratory stimulants has been associated with increased

amounts of such light and unsteady non-REM sleep, thereby counteracting the other positive effects on sleep apnea [6, 23]. Importantly, this was not the case with BCAA. Since REM sleep is generally associated with worsening of sleep apnea [4], the increased amount of REM sleep in our patients is an aspect that needs further consideration.

The mechanism of the augmented respiratory effects and changes in sleep pattern seen with BCAA infusion is unknown. Alteration in plasma amino acids with elevated levels of BCAA competing for transportation across the blood-brain barrier with amino acids, which act as precursors for neurotransmitters, has been proposed as a mechanism [11, 14]. In CRF patients this hypothesis may be of particular relevance, since both serum BCAA depletion and specific changes in cerebral uptake of amino acids have been associated with CRF [24–26].

In conclusion, BCAA was found to significantly improve ventilation during sleep, reflected by a decrease in ETCO<sub>2</sub>. This was achieved with an increased percentage of REM sleep and thus with a improvement of the disturbed sleep pattern observed in these patients. Taken as preliminary evidence, in the one patient with severe obstructive sleep apnea, the total number of apneas and the severity of desaturation in the remaining apneas and hypopneas were reduced during BCAA infusion. We think these results necessitate further investigations demonstrating whether BCAA is useful in the treatment of sleep apnea in CRF patients, and perhaps in ameliorating the sleep disorders which often accompany CRF. This improvement in sleep quality may reduce hypersomnolence and cognitive dysfunctioning during daytime, with a reduced requirement for sedative hypnotic medication, and thus enhance the patients' rehabilitation and quality of life.

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