Measurement of the hemodialysis quantity using a QCM ammonia gas sensor

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(2008 年 3 月 15 日　受理)

Abstract

Recently, expired gases are analyzed non-invasively for monitoring the substances in the blood. Breath ammonia has been shown to correlate with blood urea nitrogen (BUN) and creatinine (Cr), both of which are indicators of solute removal in hemodialysis.

In this study, breath ammonia concentration was continuously measured using a crystal oscillator Quartz Crystal Microbalance (QCM) during the expiration of patients undergoing dialysis treatment. The results show that NH_3 decreased gradually as the treatment proceeded. A strong correlation was observed between changes in the frequency of the QCM gas sensor and both the pre-dialysis BUN level ($r = 0.71$, $p < 0.05$) and the post-dialysis BUN level ($r = 0.90$, $p < 0.05$). NH_3 was found to fall precipitously during dialysis. The differences were statistically significant. In addition, we found a statistically significant correlation between BUN and NH_3 in expired gas. These results suggest that continuous measurement of NH_3 is useful to assess the status of solute removal during hemodialysis.

Key word: expired gas, non-invasively analyzed, hemodialysis, QCM, BUN, continuous measurement

1. Introduction

In Japan, the number of patients on maintenance hemodialysis was 248,166 in 2004, and it is growing by about 10,000 each year [1]. On the average, patients on hemodialysis receive 3 sessions of dialysis per week, with each session lasting 4 hours. [2]. Several reports suggest that the death rate of hemodialysis patients decreases following prolonged and frequent hemodialysis, while others have suggested that the increase in the volume of dialysis do not always improve the prognosis [3,4].

The efficiency of dialysis may be evaluated by using the index Kt/V. Kt is a product of urea clearance by hemodialysis and its duration. V is the patient's total body water. [5]. Removal of urea is not moniterd during each session of dialysis.

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Instead, it is controlled by using the mean of the values yielded from hematological test conducted one to four times a month. The findings from this monitoring represent the cumulative result of continued effort, instead of reflecting the course of treatment after each session of hemodialysis.

Under such circumstances, the authors considered that the assessment of dialysis on a real-time basis will provide information useful in determining an optimal condition of dialysis for a given patient. The previous reports show that blood ammonia levels were higher in patients with renal failure than in healthy individuals [6,7].

A large amount of ammonia is eliminated into the expired gas in hemodialysis patients . [8]

It is therefore predicted that measurement of NH_3 level in expired gas reflects the course of elute removal during hemodialysis, in particular the effectiveness of removal of such substances. Furthermore, the course of elute removal is expected to correlate with the duration of hemodialysis. In this regard, the monitoring NH_3 on a real-time basis will be useful in continuing optimum and safe hemodialysis.

2. Subjects

The study involved 20 patients on hemodialysis. There were 16 men and 4 women, with a mean age of and a mean duration of dialysis being 68 ± 16.5 years, and 5.3 ± 9.5 years, respectively. The underlying disease was chronic glomerulonephritis in 10, diabetic nephropathy in 6, kidney cyst in 1 , and unclassified nephritis in 1 case. A total of 10 hospital employees and volunteer students free of hepatic or renal disease served as the control group.

This study was approved by the Tokatsu Clinic Ethics Committee prior to its start.

The correlation coefficients (r) between expired NH_3 level and blood BUN levels were calculated both before and after hemodialysis , as were those between expired NH_3 level and blood Cr levels. The significance of each correlation was tested against the null hypothesis (p). In addition, a correlation was also analyzed between expired NH_3 levels measured with the QCM gas sensor and those measured with a photacoustic multiple gas monitor. Fig. 1 shows how measurement was performed

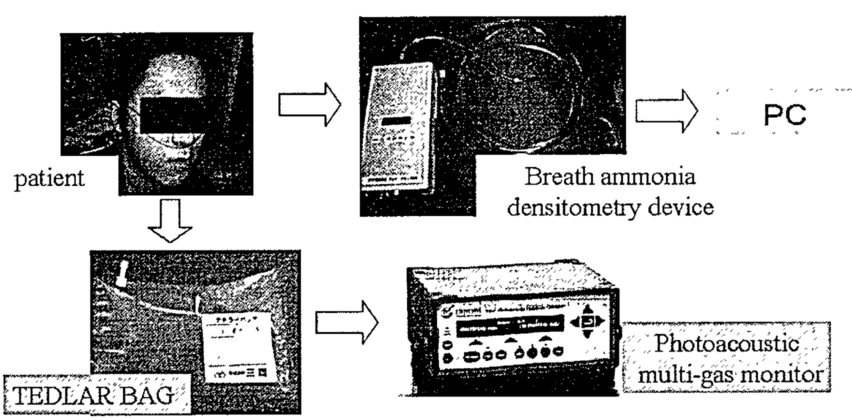

Fig. 1. Measurement with each gas monitor

using each sensor.

An analysis using the QCM gas sensor was performed on 4 subjects, while measurements with the photoacoustic multiple gas monitor were carried out on 20 subjects. The latter 20 subjects underwent also BUN analysis. Simultaneous measurements using both the QCM gas sensor and the photoacoustic multiple gas monitor were carried out on one subject.

3. Methods

Because NH_3 level in expired gas can be measured non-invasively, it is easy to measure this parameter during each session of hemodialysis. For this reason, this study was undertaken to try continuous monitoring of expired gas NH_3 level using a QCM ammonia gas sensor (SNT Co., Ltd.) composed of a quartz oscillator chip combined with a reactive membrane specific to ammonia [9]. The data from this measurement were compared with the results of intermittent measurement of expired NH_3 level using a photoacoustic multiple gas monitor (Photoacoustic Field Gas-Monitor 1412, INNOVA Tech Instruments).

3-1 QCM gas sensor

The QCM gas sensor is composed of a quartz oscillator chip combined with a gas adsorptive membrane and is designed to sense gas through detection of reduction in the resonance frequency of the quartz oscillator due to the mass load effect of gas adsorbed onto the membrane [10].

A quartz oscillator shows a reduction in resonance frequency proportional to the mass of the substance adsorbed onto the quarts oscillator chip. This nature of quartz oscillator can be utilized to measure the mass of the substance adsorbed onto the quartz oscillator chip [11]. Changes in resonance frequency (Δf) are defined by the following equation [12].

$$\Delta f = -2 f_0^2 \Delta m / A (\rho_q \mu_q)^{1/2} \qquad (1)$$

where f_0 denotes the resonance frequency, Δm indicates a change in the mass of the reactive membrane following adsorption of ammonia, ρ_q and μ_q denote the density and shear stress of quartz, and A indicates the electrode area of the quartz oscillator.

Equation (1) indicates that when the mass of the reactive membrane on the quartz oscillator chip increases following adsorption of gas, the resonance frequency changes proportionally to the mass of the adsorbed gas.

In this study, the reactive membrane was made of zirconium phosphate (ZrP). ZrP can selectively adsorb gases of the amine family and can therefore be used in preparing a sensor selectively reacting with ammonia [13]. Because ZrP is a compound of a layered structure, we freed it and made it into thin pieces to increase the surface area and reactive potentials [14,15]. Furthermore, a temperature and humidity sensor was incorporated into the sensor, so that the influence from temperature and relative humidity can be eliminated from analysis, using an equation for correction [16]. Fig. 2 shows the structure of the QCM gas sensor. Its specifications were as follows: range of measurement 0.10 to 10 ppm, accuracy ± 0.1ppm, temperature range 5℃ to 40℃, gas collection by automated aspiration with a micro-fan, and sensing latency within few seconds (90% response time).

For measurement with the QCM gas sensor, a tube was attached to the nose of

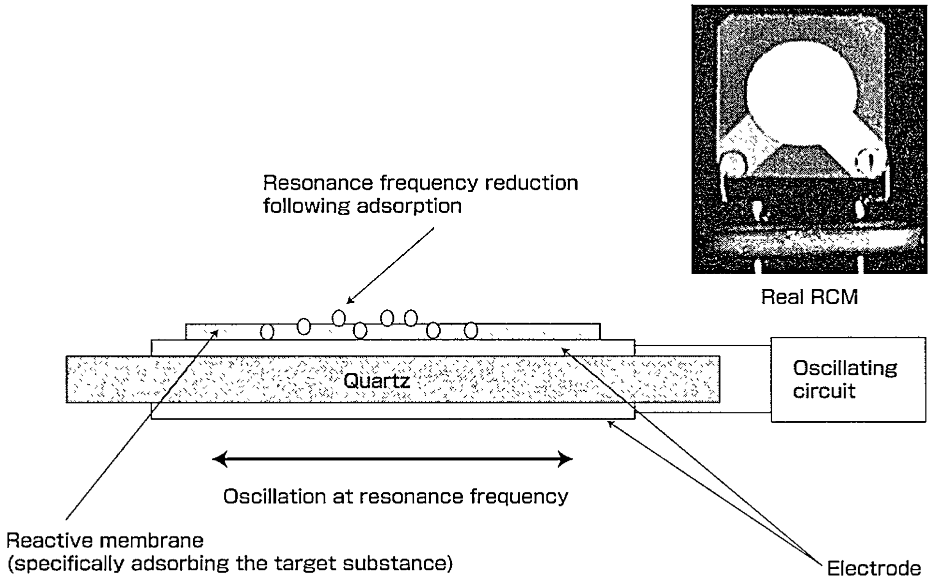

Fig. 2. QCM gas sensor

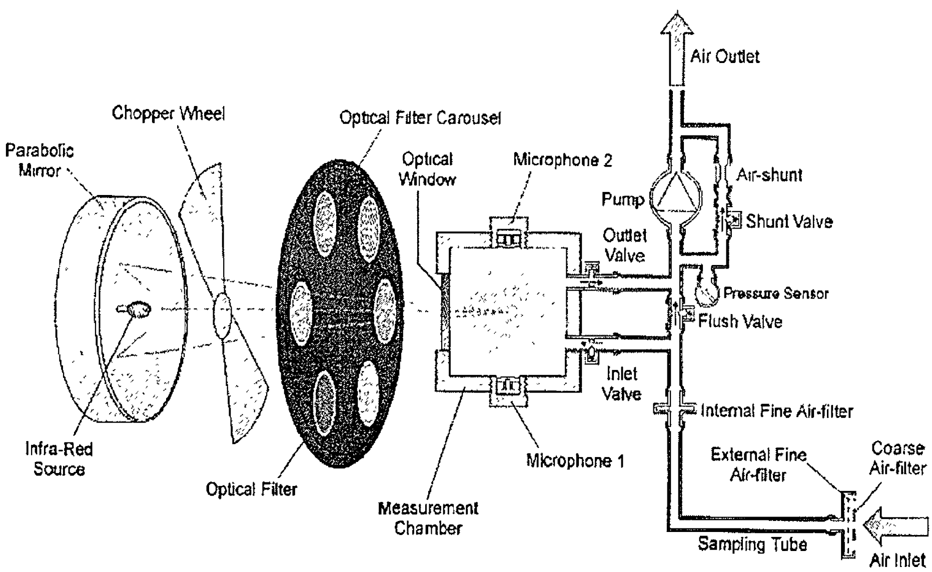

Fig. 3. Outline of photoacoustic multiple gas sensor

each patient during hemodialysis, to monitor expired gas NH_3 level continuously from the start to end of hemodialysis. The NH_3 levels thus measured were compared to the data on blood urea nitrogen (BUN) levels measured before and after hemodialysis.

3-2 Photoacoustic multiple gas monitor

Fig. 3 shows the photoacoustic multiple gas monitor used for intermittent measurement of NH_3 level in expired gas.

In photoacoustic measurement [17], infrared ray passes through the optical filter if ammonia is present within the chamber. When ammonia is exposed to light, its molecule is excited by the photo-energy resulting in unstable excitation. If irradiation is discontinued seconds Δt later, the ammonia molecule changes from unstable excitated to stable basal condition. The absorbed energy is released in the form of heat, elevating the temperature within the chamber by ΔT .According to the rule of ideal gas, pressure is elevated to a degree corresponding to the degree of temperature rise with the volume being constant, resulting in pulse-wise radiation of light and a pulse-wise elevation of pressure. Therefore, if light is applied in a pulse-wise manner, a change in pressure of a frequency equal to the frequency of light takes place, resulting in generation of sound. Because the level of energy released from the molecules is proportional to the number of molecules, the intensity of the signal caught with a microphone is linearly proportional to the sample concentration. Therefore, the NH_3 concentration and the intensity of the detected signal show a proportional relationship defined by the following equation, if signal is denoted as S.

$$S=nCp \qquad (2)$$

In this equation, n indicates the constant determined by the pulse frequency of the source, C denotes the number of gas molecules exposed to the light at a given concentration of the gas, and P indicates the level of the light source. The specification of the photoacoustic multiple gas monitor used were: sensitivity being 10ppb to 1ppm and sampling interval being 13 seconds.

During measurement, each patient on hemodialysis exhaled 1 L of breath into a Tedlar bag, and NH_3 level in the collected expired gas was measured intermittently, using a photoacoustic multiple gas monitor. Measurements were done twice (before and after dialysis) for comparison with BUN and creatinine (Cr) levels.

Simultaneous measurements using both the photoacoustic multiple gas monitor and the QCM gas sensor were carried out 5 times (immediately before and every one hour after the start of 4-hour dialysis). The data from these measurements were compared with the data from hematological tests conducted before and after dialysis.

4. Results

4-1 Blood BUN and Cr levels before and after dialysis in hemodialysis patients

Fig. 4 shows the BUN and Cr levels before and after dialysis in hemodialysis patients and in healthy volunteer. In the

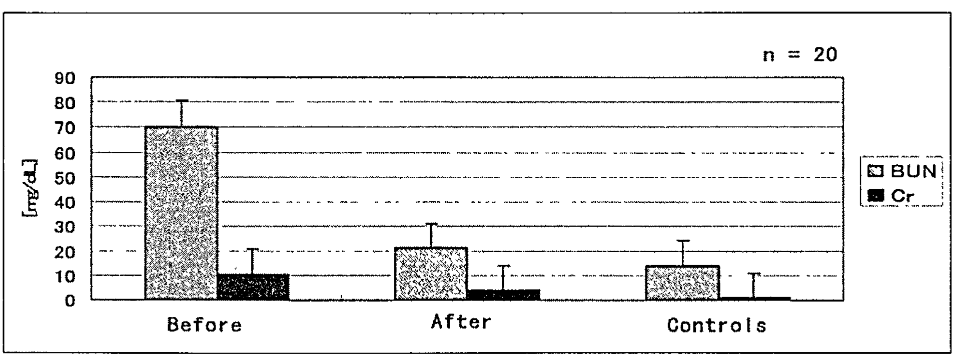

Fig. 4. Comparison of BUN and Cr levels before and after hemodialysis

hemodialysis group, BUN levels were 78 ± 24.5 mg/dL before dialysis and 22 ± 12 mg/dL after dialysis, and Cr level were 10.6 mg/dL before dialysis and 3.8 mg/dL after dialysis. In the control group [18], BUN levels were 14 mg/dL ± and Cr levels were 0.5 mg/dL ± . Thus, both BUN and Cr levels were higher in the hemodialysis group than in the control group. It was confirmed that BUN and Cr were effectively eliminated by hemodialysis. The mean of the criterion range of BUN level (8-20 mg/dL) served as the BUN level for the healthy controls (14 mg/dL), and the mean of the criterion range for adult men (0.6-1.0 mg/dL) served as the Cr level for the healthy controls (0.8 mg/dL) in this study. [18]

4-2 Comparison of pre- and post-dialysis expired gas NH_3 levels (measured with the photoacoustic multiple gas monitor) with blood BUN and Cr levels

Fig. 5(A) shows the results of measurements with the photoacoustic multiple gas monitor before and after dialysis. The expired gas NH_3 level in hemodialysis patients, as measured using the photoacoustic multiple gas monitor, tended to rise as the blood BUN level became higher. Both expired gas NH_3 level and blood BUN level decreased after hemodialysis.

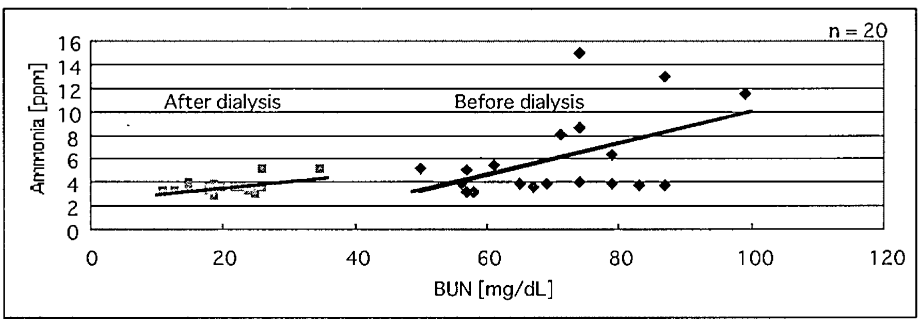

Fig. 5(A) Relationship between BUN level and expired gas NH_3 level measured with a photoacoustic multiple gas monitor

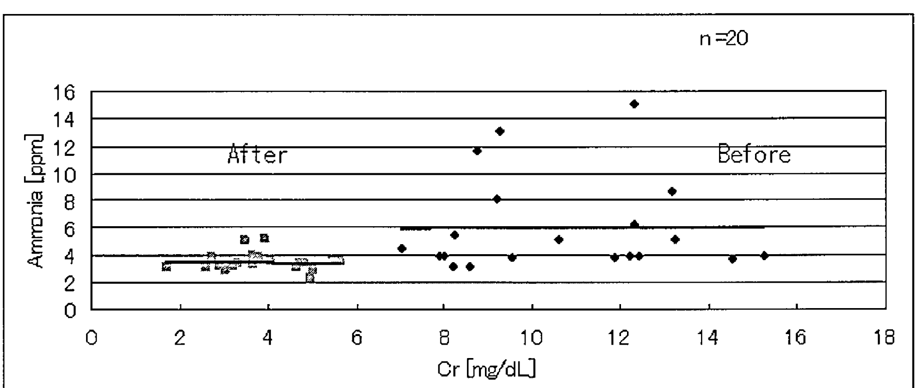

Fig. 5(B) Relationship between Cr level and expired gas NH_3 level measured with a photoacoustic multiple gas monitor

The correlation coefficient (r) between pre-dialysis expired gas NH_3 level and blood BUN level was 0.48 ($p < 0.05$), and that between post-dialysis expired gas NH_3 level and blood BUN level was 0.49 ($p < 0.05$). Thus, a weak correlation was noted between these two parameters both before and after dialysis. However, blood Cr level did not correlate significantly with pre-dialysis expired gas NH_3 level ($r = 0.0095$, $p > 0.05$) or post-dialysis expired gas NH_3 level ($r = -0.06$, $p > 0.06$). As shown in Fig. 5(B)

4-3 Relationship between BUN level and the frequency change of the QCM gas sensor before and after dialysis

As shown in Fig. 6, a strong correlation was noted between changes in the frequency of the QCM gas sensor and both the pre-dialysis BUN level ($r = 0.71$, $p < 0.05$) and the post-dialysis BUN level ($r = 0.90$, $p < 0.05$).

4-4 Simultaneous measurement using both the QCM gas sensor and the photoacoustic multiple gas monitor

Fig. 7 shows a result of simultaneous measurements using both the QCM gas sensor and the photoacoustic multiple gas monitor. The readings from the QCM gas sensor were similar to those from the photoacoustic multiple gas monitor, allowing us to confirm that the QCM gas monitor was capable of continuously monitoring expired gas NH_3 level. It was also confirmed that the expired gas NH_3 level decreased over time during hemodialysis.

5. Discussion

Ammonia in the body is produced in the intestine, kidneys, liver, and muscles. The ammonia produced in vivo is converted into urea in the liver by means of a urea cycle, and it then combines to H^+ in the kidneys to be released into urine in the form of NH_4^+. The majority of ammonia in the blood of healthy individuals originates from the intestine. Because the ammonia produced in the intestine is mostly absorbed into blood, converted to urea in the liver, and eliminated, blood ammonia level is usually low [19]. It has been reported that the ammonia detected in the oral cavity contains the ammonia produced in the esophagus, stomach, oral cavity, and alveoli, and that in healthy individuals, the ammonia found in the oral cavity

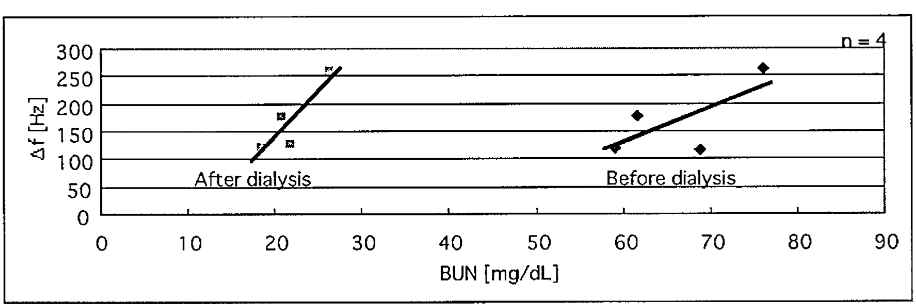

Fig. 6. Relationship between BUN level and changes in the frequency of QCM ammonia gas sensor

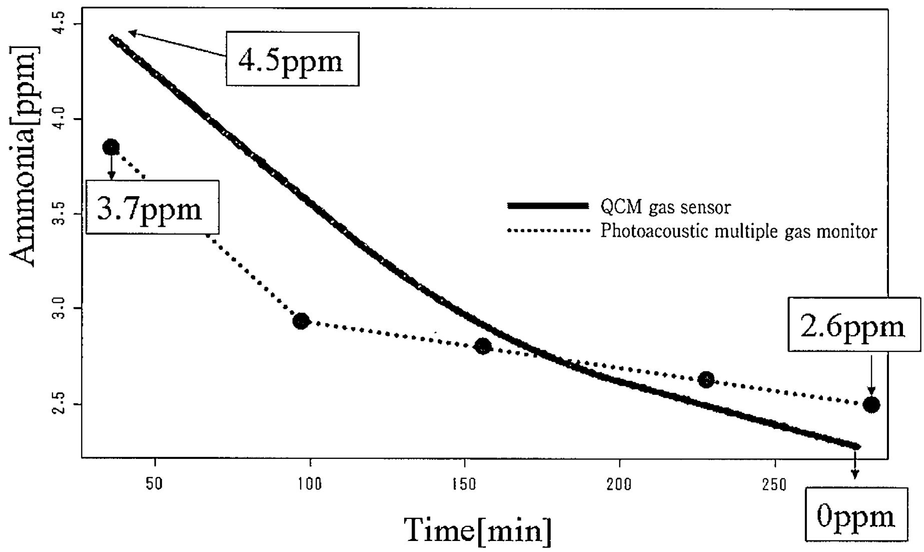

Fig. 7 Simultaneous measurement using both the QCM ammonia gas monitor and photoacoustic multiple gas monitor

originates mostly from saliva and only a very small percentage of it comes from alveoli [20]. Ammonia originating from saliva is primarily a product of degeneration of salivary urea by bacteria in the oral cavity. Because saliva-derived ammonia is reabsorbed into saliva, the concentration of ammonia gas in the oral cavity is low [21]. It has also been reported that the oral cavity ammonia level showed only slight elevation in Helicobacter pylori-positive patients [22]. On the basis of these previous findings, we may say that NH_3 level in expired gas from hemodialysis patients primarily originates from the alveoli.

We analyzed the results of measurement of expired gas NH_3 levels using the photoacoustic multiple gas monitor and the QCM gas sensor. The analysis revealed that measurement of expired gas NH_3 level can substitute measurement of BUN level. However, there was no marked correlation between Cr level and expired gas NH_3 level, suggesting it unlikely that expired gas NH_3 level may be used as a substitute of Cr level. This result as to Cr seems to reflect the facts that Cr level differs significantly between man and women, and that it is also affected by muscular mass. As for the Cr level, an infant and a lardy figure show a low value, and it is known that a person of meatiness shows a high value[23]. It seems that this affected this measurement.

At present, Urea Reduction Ratio (URR) and Kt/V are often used when determining optimum dialysis volume. URR is defined by the following equation [24].

$$URR = \frac{BUN_b - BUN_a}{BUN_b} \times 100(\%) \qquad (3)$$

where BUN_a denotes pre-dialysis BUN and denotes post-dialysis BUN_b. Because both URR and Kt/V require BUN level for calculation, these parameters necessitate hematological tests conducted once to four times a month. Therefore, none of these two parameters indicate the real-time dialysis volume for or during each session of dialysis.

At present the volume of eliminated water is measured as an indicator of dialysis monitoring. However, the course of solute removal is not monitored. If BUN level can be estimated using the method proposed in this paper, without blood sampling, it may allow real-time non-invasive monitoring of dialysis volume for hemodialysis patients.

Open issues

During measurement with the QCM gas sensor, dew condensation occurred in the expired gas sampling tube. It is likely that ammonia is adsorbed onto the thus formed dew. It is therefore necessary to avoid dew condensation (by changing the tube length, heating, coating the inner surface, and/or using a filter) for more accurate measurement. It also seems necessary to improve the speed of reaction by modifying the structure of the reactive membrane, adopting an equation of correction.

Acknowledgments

The authors are grateful to Mr. Naoki Abe (SNT, Co., Ltd.), Mr. Kotaro Hiratsuka (Matsushita Techno Trading Co., Ltd.), Mr. Tomotari Matsuda (Omnisence Japan, Ltd.), Mr. Toshihisa Hoshino (Engineer, Itabashi Central General Hemopurification Center), Dr. Ryoichi Nakazawa (Tokatsu Clinic hospital), Mr. Takao Matsugane (Engineer, Tokatsu Clinic Hospital), and Dr. Kunio Suwa (Teikyo Medical Technology College) for their cooperation with this study.

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