Doctoral Thesis

Psychophysiological Study on Autonomic Nervous Response in Hemodialysis Patients

by
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Abstract

Patients who have progressed to end−stage kidney disease (ESKD) are forced to undergo dialysis treatment for life support. Dialysis treatment impacts patients' quality of life (QOL) and physical and psychological states. Therefore, therapeutic approaches for ESKD must also consider their impact on hemodialysis patients' QOL.

This thesis addresses several issues related to the complications experienced by hemodialysis patients. Hemodialysis patients have a multifaceted condition involving both physical and psychological components and substantially impacting QOL. One of the most serious complications observed in hemodialysis patients is autonomic nervous dysfunction. Autonomic dysfunction is one of the leading causes of psychologically unstable states such as depression. Therefore, better understanding the autonomic nervous activity and psychological states specific to hemodialysis patients is considered a key to improving dialysis therapy. However, knowledge about the relationship between autonomic nervous function and psychological problems in hemodialysis patients is limited.

As described in chapter II, the first goal of this research was to investigate the relationship between changes in autonomic nervous activity and physical and mental health. A hemodialysis patient is in an environment where a psychological symptom can easily arise from a physical problem due to hemodialysis complications. The psychological stress load of hemodialysis not only results from extracorporeal circulation but also endogenous factors. The author studied the relationship between autonomic function and anxiety state in healthy adults, diabetic nephropathy patients, and patients with non−diabetic nephropathy. Furthermore, photoplethysmograms recorded before and after starting hemodialysis were compared to examine whether extra−corporeal circulation influences autonomic nervous system function. Investigating the relationship between autonomic nervous response and psychological characteristics according to patients' underlying kidney diseases would be useful to reducing the inherent risks of hemodialysis. The results of applying detrended fluctuation analysis for the peak−to−peak intervals of photoplethysmography data suggested that the autonomic nervous function in patients with diabetic nephropathy does not react robustly to external factors, in part because of decreasing sympathetic

activity and increasing parasympathetic activity. Dialysis patients with diabetic nephropathy were more likely to experience depression, and their autonomic nervous system functions were affected more severely by hemodialysis than those with non−diabetic nephropathy.

Chapter III discusses the most suitable ultrafiltration rate (UFR) based on changes in autonomic nervous activity. Clinical studies have shown that excessive UFR in patients receiving regular thrice−weekly hemodialysis treatment is independently associated with an increased long−term risk of death. However, the appropriate UFR has not yet been established. Moreover, decreased heart rate variability (HRV) has been considered a risk factor for mortality in hemodialysis patients. However, there have been few reports about the most suitable UFR based on changes in autonomic nervous activity in patients without blood pressure variation. Therefore, this study assessed the most suitable UFR range from the viewpoint of autonomic nervous system function using power spectral analysis of R−R interval dynamics in patients without blood pressure variation. The results of this study have the potential to lower the risks of cardiovascular disease or sudden cardiac death during hemodialysis. Variations in autonomic nervous activity over time due to differences in UFR were evaluated by measuring HRV and approximate entropy in patients without blood pressure variation during hemodialysis sessions. Measures such as HRV and approximate entropy are important indicators of autonomic nervous activity that have been associated with establishing a suitable UFR. This study demonstrated that high UFR was associated with an increase in sympathetic nervous overactivity and suggests that hemodialysis should be performed at a UFR <15 ml/h/kg.

In chapter IV, I focus on the gut−brain axis and constipation in hemodialysis patients. Causes of constipation include lifestyle changes related to hemodialysis. Constipation in hemodialysis patients may also be associated with psychological problems and may significantly impact QOL. Hemodialysis treatment under conditions of strict dietary restriction may involve diarrhea, constipation, or both, with one occurring after the other. The prevention and control of constipation are also important because chronic constipation may substantially impact the QOL of hemodialysis patients. However, few studies have focused on the psychological changes of hemodialysis patients associated with improvement of constipation symptoms. Chapter IV describes the effect of improving constipation on changes in hemodialysis patients' QOL. I investigated the effect of enteric capsules containing *Bifidobacterium* on constipation and QOL in hemodialysis patients using the Constipation Assessment Scale (CAS) to measure the degree of constipation and the

Patient Assessment of Constipation Quality of Life Questionnaire (PAC−QOL) to measure the influence of constipation on QOL. These results suggest that the intake of enteric capsules containing *Bifidobacterium* is useful to improve the intestinal environment and QOL of hemodialysis patients, and to reduce serum phosphorus values.

Finally, chapter V summarizes the results of these studies and provides general conclusions. This body of research has been conducted in an attempt to explore the changes in autonomic nervous activity associated with undergoing hemodialysis. The resultant findings can be beneficial in terms of risk factor reduction in daily life among patients receiving hemodialysis treatment. My studies indicate that the improvement of sympathetic nervous activity and psychosocial stability may have the potential to improve hemodialysis patients' QOL. Thus, in particular, not only the primary disease that led to hemodialysis, but also constipation could evoke a poor prognosis for psychological symptoms. As autonomic dysfunction is the leading cause of psychologically unstable states such as depression, better understanding the autonomic nervous activity and psychological states specific to hemodialysis patients is considered a key to improving dialysis therapy.

The information relevant to early prediction of prognosis such as hemodialysis complications is still incompletely understood. However, the author believes that the therapeutic approach to hemodialysis patients should consider not only a patient's physical condition but also comprehensive factors including their stress level as well as psychosomatic, psychological, and social aspects. At the time of writing this dissertation, there is some evidence suggests that poor QOL is associated with mortality in hemodialysis patients. Thus, further research is necessary to assess not only the dialysis technique, but also psychological aspects of care. Improving mental health may reduce mortality and ameliorate physical function in hemodialysis patients. Therefore, the author recognizes that the ongoing refinement of hemodialysis treatment to maintain patients' psychological and physical condition suitably for their environment is essential. In the near future, the author is planning an investigation of a psychological and physical condition guidance system by measuring the change in HRV in a clinical setting.

Contents

Chapter 1

Introduction

1.1 Hemodialysis

Chronic kidney disease (CKD) involves the progressive loss of kidney function over time. At the final stage of CKD, end−stage kidney disease (ESKD), the kidney is no longer able to eliminate excess water and waste products from the patient's body. In CKD, symptoms increase in severity as the disease becomes more advanced and ultimately progresses to kidney failure. In recent years, diabetes mellitus has been identified as a major risk factor for the development and progression of CKD worldwide. Furthermore, diabetic nephropathy is the leading cause of cardiovascular disease [1].

Patients who have reached ESKD are forced to undergo dialysis treatment for life support unless they receive a renal transplant. There are two types of dialysis: hemodialysis and peritoneal dialysis. In hemodialysis, the most common type of dialysis, an artificial kidney called a dialyzer is used to remove waste and excess water from the patient's blood. Peritoneal dialysis uses the patient's peritoneum, in the abdomen, as a membrane to clear wastes and extra fluid. The primary goal of hemodialysis is to restore the intracellular and extracellular fluid environment that is characteristic of normal kidney function, which is accomplished by the transport of solutes such as urea from the blood into the dialysate and by the transport of solutes such as bicarbonate from the dialysate into the blood [2].

The population of patients receiving hemodialysis in Japan is rapidly increasing along with the prevalence of predisposing conditions such as diabetes mellitus and hypertension. According to the Japanese Society for Dialysis Therapy (JSDT), 304,856 patients were treated with dialysis therapy in Japan in 2011. Most patients, nearly 97% of the total dialysis population, received hemodialysis, whereas the remaining 3.2% (9,642 patients) were treated by peritoneal dialysis [3].

Hemodialysis commonly causes many complications in patients with kidney failure. Loss of kidney function leads to uremic syndrome, a complex phenomenon involving dysfunction of many organ systems in the body [4]. Complications can be summarized as follows: intradialytic hypotension or hypertension, complications associated with hemodialysis equipment, vascular access−related complications, cardiovascular complications, appearance of psychopathological symptoms, neurological complications, complications associated with the use of anticoagulant therapy, nausea, vomiting, itching, constipation, and others [4]. In this regard, the pathophysiology of complications in hemodialysis patients is complicated.

1.2 Psychological state of hemodialysis patients

Due to the close relationship between the mind and body, emotions can cause somatic symptoms. Conversely, somatic changes such as pain can cause psychological changes or reactions. CKD is a multifaceted problem with both physical and psychological implications for the patient [5]. Hemodialysis patients have reactive psychiatric symptoms due to the restriction of food and moisture, time bound by hemodialysis, and complications such as pain. Therefore, hemodialysis patients present signs of physical and psychological stress such as depression, anxiety, suicide, uncooperative behavior, sexual dysfunction, and psychosis [6].

Depression is the most frequent psychiatric symptom among hemodialysis patients [6]. Depression conventionally occurs in patients who have just begun hemodialysis treatment and tends to resolve in the maintenance phase. Despite the long−term survival benefit to patients resulting from advances in medical technology, depression symptoms can still be present. In recent years, it has become a focus of dialysis therapy to minimize systemic complications that appear along with the long−term reduction in QOL.

1.3 Autonomic nervous system dysfunction

Neurological complications affect hemodialysis patients and are important contributors to morbidity and mortality in patients with renal failure [7]. Among them, the author particularly focused on complications in hemodialysis patients involving the autonomic nervous system, because hemodialysis is known to induce autonomic nervous system dysfunction. Autonomic nervous system dysfunction occurs in over 50% of hemodialysis patients [8]. The autonomic nervous system regulates and controls bodily functions that affect almost all body systems including gastrointestinal system, genitourinary system, respiratory system, and others.

Autonomic nervous system dysfunction may cause a variety of symptoms in hemodialysis patients. Among them, intradialytic hypotension associated with cardiac disorders is a particularly frequent and troubling side effect. Hemodialysis−induced hypotension is caused by paradoxical withdrawal of sympathetic vasoconstrictor

drive, leading to vasodepressor syncope [9]. Intradialytic hypotension can result in cerebral hypoperfusion and cerebrovascular accident. A number of studies have attempted to evaluated the autonomic nervous activity of hemodialysis patients [10−14]. Heart rate variability (HRV) provides useful information on autonomic nervous system regulation of cardiac activity in clinical settings. Three components of HRV as an indicator of self−regulatory capacity provide information on different physiological mechanisms: the high−frequency (HF) band reflects the effects of respiration on heart rate; the low−frequency (LF) band represents oscillations related to regulation of blood pressure and vasomotor tone; and the very low−frequency (VLF) band is thought to relate, among other factors, to thermoregulation and kidney function [15]. Spectral analysis of HRV is widely used to assess the sympathetic and parasympathetic functions of the autonomic nervous system [16]. Some earlier studies have reported significant reduction of HRV in hemodialysis patients [17].

1.4 Gastrointestinal disorders in hemodialysis patients

Symptoms of gastrointestinal distress, such as gas in the gastrointestinal tract, bloating, nausea, heartburn, indigestion, dyspepsia, and constipation, are common complications among hemodialysis patients [18]. A previous study reported that more than half of patients on hemodialysis experienced constipation [19]. Constipation in hemodialysis patients is often accompanied by anxiety and typically characterized by difficult or painful evacuation. Constipation can cause many complaints and symptoms of underlying problems. Furthermore, constipation in hemodialysis patients not only reduces QOL but could lead to necrosis or intestinal perforation. Intestinal perforation carries a high risk of mortality in patients undergoing hemodialysis [20].

In recent years, the “gut−brain axis,” which includes the central nervous system, has been shown to monitor and integrate gut functions as well as to link emotional and cognitive centers of the brain with peripheral intestinal functions and mechanisms [21]. Causes of constipation include lifestyle changes related to hemodialysis. Constipation in hemodialysis patients may also be associated with psychological problems and may significantly impact QOL. Therefore, minimizing the risk of constipation is clinically very important.

The symptoms associated with constipation are often intermittent and mild, and they may be chronic, difficult to treat, and debilitating [22]. Thus, hemodialysis patients with constipation warrant greater attention from the perspective of both physical and psychological aspects.

1.5 Thesis outline

This thesis has three main themes, all of which are important for assessing hemodialysis patients through psychophysiological examination. These three themes are outlined individually in the following four sections.

In Chapter II, I examined whether or not extracorporeal circulation influences autonomic nervous system function in patients with CKD by photoplethysmogram recording in conjunction with the evaluation of psychosomatic symptoms and anxiety states using the General Health Questionnaire (GHQ–28) and the State–Trait Anxiety Inventory (STAI), respectively, to investigate the relationship between autonomic nervous activity and anxiety state.

In Chapter III, I focused on the autonomic nervous activity which may be the most varied vigorously during hemodialysis with changing blood pressure due to a decrease in blood osmotic pressure and intravascular volume with water and solute removal. A number of studies have addressed the effect of blood pressure variation on autonomic nervous activity during maintenance hemodialysis. However, few studies have focused on the relationship between autonomic nervous system imbalance and ultrafiltration rate (UFR) in patients on maintenance hemodialysis without blood pressure variation, despite autonomic nervous system activation being proposed as an important factor for maintaining blood pressure during hemodialysis. Variations in autonomic nervous activity over time due to differences in UFR were evaluated by measuring heart rate variability (HRV) and approximate entropy.

In Chapter IV, I investigated the effect of improving constipation on QOL in hemodialysis patients. Psycho−neuro modulation through the brain–gut axis likely plays an important role in patients' daily stress arising from hemodialysis−related psychological complications and chronic constipation.

Chapter II

Evaluation of Autonomic Nervous Activity by DFA

2.1 Introduction

Hemodialysis is a medical treatment for patients in end−stage kidney disease (ESKD). Healthy people have two kidneys, which are bean−shaped organs are located in the mid−back. Normal healthy kidneys perform at least 5 major functions essential to maintaining our general health. The primary function of the kidney is to remove excess water and waste products from the body. Each kidney processes approximately 150−180 liters of urine from blood every day without rest. The kidney also produces erythropoietin, regulates blood pressure, and activates vitamin D. As kidney function decreases, uremic toxins and excess water in the body increase. Hemodialysis is a process that removes accumulated solute from a patient who has total or near−total loss of kidney function, as indicated by blood tests such as creatinine level. During hemodialysis, the patient's blood is circulated through a dialyzer containing a physiological salt solution (dialysate). Solute from the blood diffuses into the dialysate, which is separated from the blood by a thin semipermeable membrane, the major component of the dialyzer [23].

The number of diabetic nephropathy patients on hemodialysis has been steadily increasing in Japan. In December 2011, 38,893 patients started hemodialysis, among whom 16,971 had diabetic nephropathy [24]. Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria, arterial blood pressure elevation, a steady decline in glomerular filtration rate, and a high risk of cardiovascular morbidity and mortality [25]. Diabetic autonomic neuropathy is a serious and common complication of diabetes. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, and hypoglycemic autonomic failure [26].

Diabetic autonomic neuropathy is particularly caused by factors related to vascular and metabolic disorders. Persistent hyperglycemia causes axonal degeneration of nerve fibers. In addition, hypoxia−ischemia due to circulatory disorders affects the autonomic nervous system and sensory nerves. The basic rhythm of periodic phenomena, such as heart rate and blood pressure, is governed by the autonomic nervous system. Dysfunction of the autonomic nervous system has also been recognized in patients with chronic kidney disease [27].

Heart rate variability is affected by a signal from the central nervous system and internal sensory nerves. The autonomic nervous system is a part of the nervous system

that automatically regulates physiological processes in the body without conscious control. It is divided into two functions: the sympathetic nervous system and the parasympathetic nervous system [28].

The quantitative evaluation of autonomic nervous system activity based on HRV has been used to assess autonomic function and stress analysis of the frequency component and fluctuation component [29]. Pulse waves are considered to result from multiple factors, with fingertip blood flow fluctuations occurring through the activity of the sympathetic nerves and vascular smooth muscle of the cardiac autonomic structures of the fingertip. The trend component is included in the time series data of the pulse wave. A period analysis is used to measure biological signals such as the fluctuation component, which is applied to the evaluation of the physiological changes in the autonomic nervous system.

Hemodialysis patients are susceptible to psychological symptoms due to physical problems arising from hemodialysis complications. Psychological stress caused by hemodialysis is not only related to extracorporeal circulation but also to endogenous factors. Therefore, autonomic nervous function is affected by endogenous psychological changes during hemodialysis. In other words, hemodialysis patients, especially those with diabetic nephropathy, are in a state of high anxiety and poor physical and mental health, and their autonomic nervous systems are deteriorated.

The aim of this study was to investigate the relations among changes in autonomic nervous activity, physical and mental health, and anxiety state in healthy adults, diabetic nephropathy patients, and patients with non−diabetic nephropathy. I also examined whether extracorporeal circulation influences autonomic nervous system function by 10−minute photoplethysmogram recordings just before and after starting hemodialysis.

2.2 Methods

2.2.1 Subjects

Subjects consisted of 14 healthy adults as a control group, 7 patients with type 2 diabetes mellitus (DM), and 7 patients without diabetes mellitus (non−DM). The subjects suffering from chronic kidney disease had received maintenance

hemodialysis for more than 1 year on an outpatient basis at Yodogawa Christian Hospital Dialysis Center. No subject taking any α or β blocker, having any indwelling pacemaker, or diagnosed with any other medical disorder was included in this research. The healthy adults had no history or symptoms of heart disease, hypertension, or diabetes, and findings were normal on clinical examination. I received informed consent from all subjects. The study protocol was approved by the Ethics Committee of the Yodogawa Christian Hospital.

2.2.2 Photoplethysmography recording

Photoplethysmography was used to measure the physiological signals during the hemodialysis session, because pulse waves can be continuously measured without affecting patient conditions or the hemodialysis procedure. Photoplethysmography was performed using a BACS detector II (CCI Co.) with the sensor located at the cuticle of the second digit of the hand contralateral to the location of vascular access in hemodialysis patients. The photoplethysmography data were measured every 10 minutes before and after starting the hemodialysis session, with the patient in a relaxed supine position. The photoplethysmography data were digitally sampled at 200 Hz, and the noise was removed with a FIR filter (0.8−12.0 Hz) using MATLAB ver. 2010b. Figure 2.1 shows the relationship between the R−R interval of the electrocardiographic waveform and P−P interval of the photoplethysmogram waveform in the cardiac conduction system. In the present study, peak−to−peak intervals of the photoplethysmography data were extracted and treated as P−P variability using MATLAB ver. 2010b software.

2.2.3 Frequency−domain measures

In general, the mean value of all R−R intervals in the electrocardiogram (ECG) has been used as a frequency domain measurement of HRV. In this study, the P−P interval corresponds to the R−R interval. In the frequency domain, the power spectra were categorized into 1) high−frequency (HF: 0.15−0.4 Hz), 2) low−frequency (LF: 0.04−0.15 Hz), and 3) very low−frequency (VLF: 0.003−0.04 Hz) component bandwidths, with all frequency−domain components expressed in absolute units (m^2) (Figure 2.2) [15]. Power spectral analysis recognizes three main components: HF

reflects parasympathetic activity and LF reflects parasympathetic and sympathetic activity. The ratio of low− to high−frequency powers (LF/HF) reflects sympathetic activity.

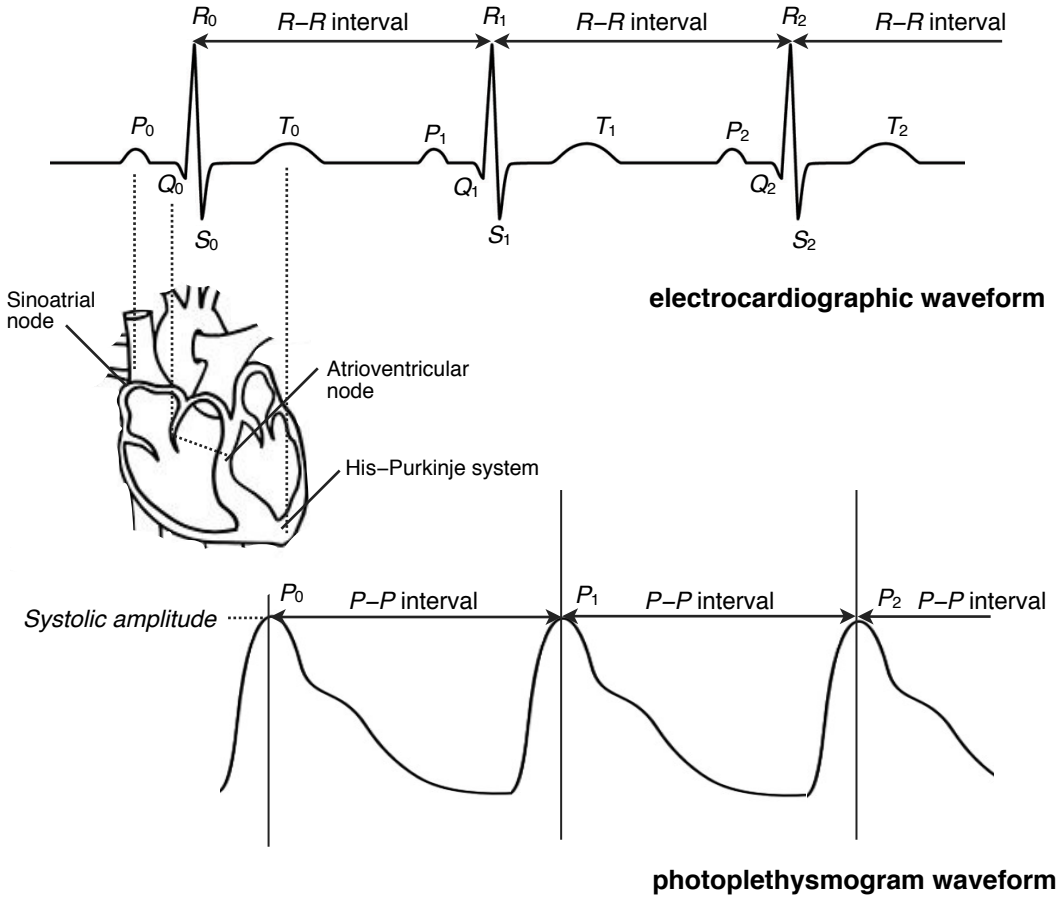

Figure 2.1 Relationship between R−R interval of electrocardiographic waveform and P−P interval of photoplethysmogram waveform in cardiac conduction system

In this study, peak−to−peak intervals of the photoplethysmography data were extracted and treated as P−P variability.

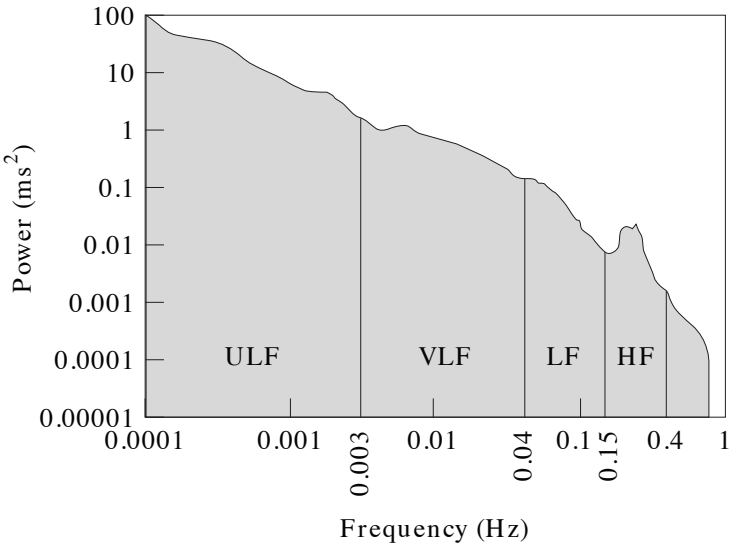

Figure 2.2 Power spectral density of heart rate variability (Reprinted from [15])

Reprinted from the Heart rate variability. Standards of measurement, physiological interpretation, and clinical use [15].

2.2.4 Fractal scaling measures

Detrended fluctuation analysis (DFA) was first proposed by C.K. Peng in 1995 and has been widely used to quantify the complexity of signals using the fractal property [30−31]. DFA is a modified root mean square method for the random walk. The mean−square distance of the signal from the local trend line is analyzed as a function of scale parameter and avoids the spurious detection of apparent self−similarity [32]. DFA it typically used to quantify the fractal scaling properties of R−R intervals, known as HRV. This method has been applied to a wide range of simulated and physiological time series [33].

In this study, I applied DFA to the analysis of photoplethysmography data. This algorithm determines the scaling behavior of the time series based on the computation of a scaling exponent α, from a discrete−time process with length N samples. For HRV signals, $x(n)$ is the n^{th} P−P interval between consecutive beats in a photoplethysmograph. The DFA procedure consists of four steps.

First, the time series is integrated as follows:

$$y(k) = \sum_{i=1}^{k} (x(i) - \bar{x}) \tag{2.1}$$

where $x(i)$ is the i^{th} signal and $\bar{x}$ is the average value of N samples. Next, the integrated time series are divided into boxes of equal length n, and a least−squares line is fit to the data (representing the trend in the box). The y−coordinate of the straight line segments is denoted by $y_n(k)$. Then, data $y(k)$ is detrended by subtracting the local trend $y_n(k)$ in each box. The root mean square fluctuation of this integrated and detrended data is calculated by Eq. (2.2).

$$F(n) = \sqrt{1/N \sum_{k=1}^{N} [y(k) - y_n(k)]^2} \tag{2.2}$$

In this study, the box size ranged from 4 to 300 beats. A box size larger than 300 beats would give a less accurate fluctuation value because of the finite length effects of data. The fluctuations can be characterized by a scaling exponent α, the slope of the line relating log $F(n)$ to log (n). Linear dependence indicates the presence of self fluctuations and the slope of the line $F(n)$ determines the scaling exponent α [34].

$$F(n) \sim n^{\alpha} \tag{2.3}$$

α is the single exponent describing the correlation properties of the entire range of the data with α = 0.5 corresponding to white noise, α = 1 representing 1/*f* noise, and α = 1.5 indicating Brownian noise or random walk (Table 2.1). A good linear fit of the log $F(n)$ to log (n) (DFA plot) indicates that $F(n)$ is proportional to $n\alpha$. The signals have been found to show bi−scaling (bi−fractal) behavior. Therefore, two scaling exponents are needed in order to characterize the fractal correlation properties of the signal. One exponent is short−term, denoted by α_1, and the other is long−term, denoted by α_2. Practically, α_1 is estimated by fitting a regression line to log $F(n)$ vs.

log n, for $4 \leq n \leq 16$, and α_2 is obtained for $16 \leq n \leq 64$. For very large scales, $n > 64$, F(n) is statistically unreliable because the number of segments Ns for the averaging procedure is very small [35].

Figure 2.3 shows an example of the photoplethysmography time series signal of P−P interval. Figure 2.4 shows an example of the double logarithmic graph log F(n) vs. log n of DFA. The slope of the lines determines the scaling exponents.

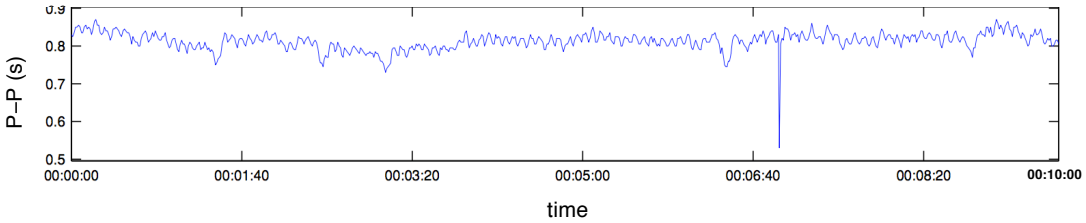

Figure 2.3 An example of the photoplethysmography time series signal of P−P interval

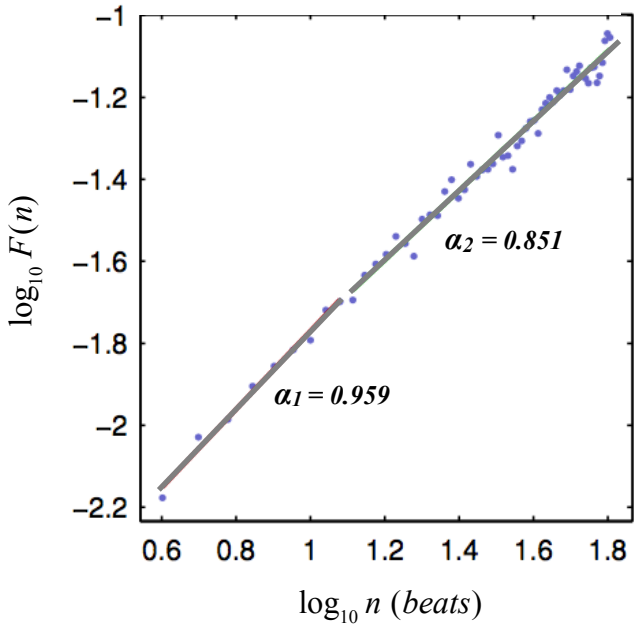

Figure 2.4 An example of the scaling exponent, short−range scaling exponent α_1 and long−range scaling exponent α_2, for P−P interval in photoplethysmography

An example of the double logarithmic graph log F(n) vs. log n of DFA.

Table 2.1 The autocorrelation of the parameter α (scaling exponent)

1. $\alpha < 0.5$	anti−correlated
2. $\alpha = 0.5$	uncorrelated signal (white noise)
3. $\alpha > 0.5$	positive autocorrelation in the sigal
4. $\alpha = 1$	1/*f* noise
5. $\alpha = 1.5$	Brownian noise or random walk

The fluctuations can be characterized by a scaling exponent α. The value of α represents the degree of correlation in the signal. $\alpha = 0.5$ indicates the signal is uncorrelated (white noise); $0.5 < \alpha < 1.0$ indicates the signal is positive correlated; $0 < \alpha < 0.5$ indicates the signal is negative correlated; $\alpha = 1.0$ corresponds to 1/*f* noise and $\alpha = 1.5$ corresponds to Brownian noise or random walk.

The two scaling exponents α_1 and α_2 were determined as the crossover point [36] that discriminates the short−range (α_1) and long−range (α_2) scaling exponents. A previous study found that the scaling exponent α determined by means of DFA in healthy young subjects had an interbeat time series with a fractal scaling exponent. Conversely, in the case of healthy older subjects, the interbeat interval time series had two scaling regions: over the short−range, the interbeat interval fluctuation resembled a random walk process, whereas comparing the short range pattern to the long range pattern (Figure 2.5) [37].

In this study, the ratio of α_1 and α_2 was used as an index representing the degree of crossover phenomenon. Equations (2.4)−(2.6) show the ratio of α_1 and α_2. Equation (2.4) represents reverse crossover. Equation (2.5) shows in which crossover does not occur. Equation (2.6) shows that the crossover phenomena did occur.

$$\alpha_1 / \alpha_2 < 1 \tag{2.4}$$

$$\alpha_1 / \alpha_2 = 1 \tag{2.5}$$

$$\alpha_1 / \alpha_2 > 1 \tag{2.6}$$

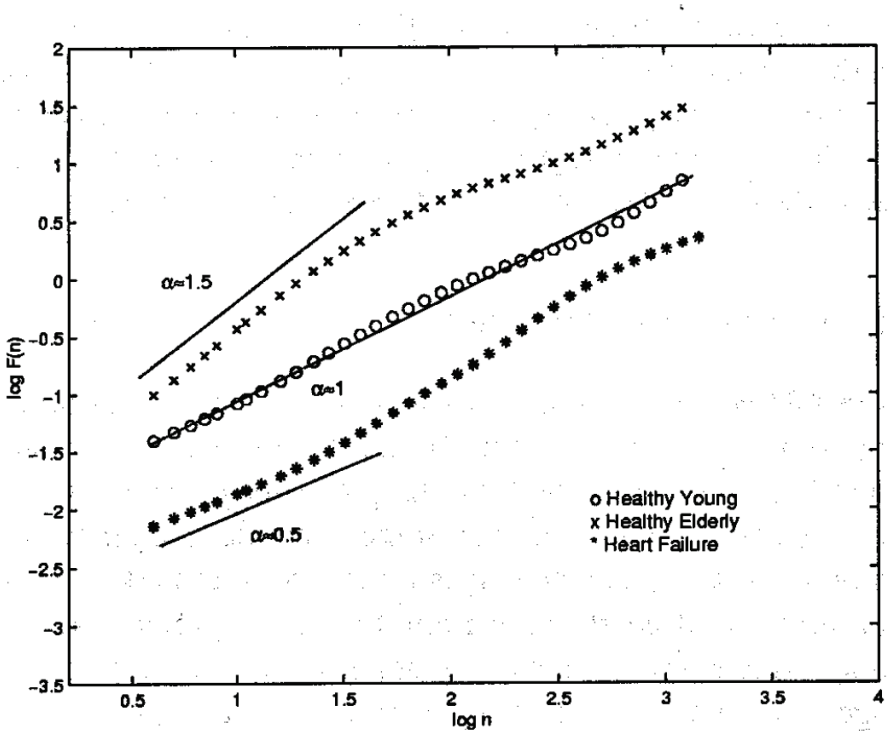

Figure 2.5 DFA analysis for three caused interbeat series (Reprinted from [37])

The value of α represents the degree of correlation in the signal. Healthy young subject (○), healthy elderly subject (×) and a patients with congestive heart failure [37].

2.2.5 GHQ−28

The General Health Questionnaire (GHQ) was originally designed to identify neurotic patients among the general patient population [38]. The General Health Questionnaire−28 (GHQ−28), a shorter version of the original GHQ, is a 28−item self−administered tool to detect non−psychotic psychiatric illnesses. It was principally designed as a test to screen for somatic symptoms, anxiety and insomnia, severe depression, and social dysfunction [39]. The GHQ−28 has four subscales of seven items each: somatic symptoms (subscale A, items 1–7), anxiety and insomnia (subscale B, 8–14), social dysfunction (subscale C, 15–21), and severe depression

(subscale D, 22–28) (Table 2.2). The Japanese version of the GHQ was translated by Nakagawa et al. and has been standardized in Japan (Table 2.3) [40]. The cutoff score for the GHQ−28 was set at 7, based on the results of an epidemiological study that distinguished psychiatric illness from healthy mental states among Japanese people [41].

In the present study, subjects' psychosomatic symptoms were evaluated using the GHQ−28. Correlations and differences in GHQ−28 scores between the groups were statistically analyzed by using non−parametric Kruskal−Wallis analysis of variance. Results were considered statistically significant at *P* values less than 0.05.

2.2.6 STAI

The Spielberger State−Trait Anxiety Inventory (STAI) is a well−known tool used to measure a subject's current level of tension and apprehension (Y−1 form−state anxiety) as well as relatively stable anxiety proneness (Y−2 form−trait anxiety) [42]. The 20 items are each scored on a scale of 0–3; higher scores indicate higher anxiety (Tables 2.4 and 2.5). Subjects were asked to consider their state and trait anxiety before completing the survey. Questions were asked as follows for the Y−1 and Y−2 forms [43].

Y−1 form−state anxiety

A number of statements that people have used to describe themselves are given below; Read each statement and then circle the appropriate number to the right of the statement to indicate how you can feel right now, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that seems to describe your present feelings best.

Y−2 form−trait anxiety

A number of statements that people have used to describe themselves are given below; Read each statement and then circle the appropriate number to the right of the statement to indicate how you generally feel. Do not spend too much time on any one statement but give the answer that seems to describe how you generally feel.

Correlations and differences in STAI between the groups were measured by using non−parametric Kruskal−Wallis analysis of variance. Results were considered statistically significant at *P* values less than 0.05.

Table 2.2 The General Health Questionnaire [38]

Have you:	Score
Subscale (A) Somatic	
1. Been feeling perfectly well and in good health?	better than usual / same as usual
2. Been feeling in need of a good tonic?	better than usual / same as usual
3. Been feeling run down and out of sorts?	better than usual / same as usual
4. Felt that you are ill?	better than usual / same as usual
5. Been getting any pains in your head?	better than usual / same as usual
6. Been getting a feeling of tightness or pressure in your head?	better than usual / same as usual
7. Been having hot or cold spells?	better than usual / same as usual
Subscale (B) Anxiety and Insomnia	
8. Lost much sleep over worry?	better than usual / same as usual
9. Had difficulty in staying asleep once you are off?	better than usual / same as usual
10. Felt constantly under strain?	better than usual / same as usual
11. Been getting edgy and bad-tempered?	better than usual / same as usual
12. Been getting scared or panicky for no good reason?	better than usual / same as usual
13. Found everything getting on top of you?	better than usual / same as usual
14. Been feeling nervous or strung-up all the time?	better than usual / same as usual
Subscale(C) Social dysfunction	
15. Been managing to keep yourself busy and occupied?	better than usual / same as usual
16. Been taking longer over the things you do?	better than usual / same as usual
17. Felt on the whole you were doing things well?	better than usual / same as usual
18. Been satisfied with the way you've carried out your tasks?	better than usual / same as usual
19. Felt you are playing a useful part in things?	better than usual / same as usual
20. Felt capable of making decisions about things?	better than usual / same as usual
21. Been able to enjoy your normal day-to-day activities?	better than usual / same as usual
Subscale (D) Severe depression	
22. Been thinking of yourself as a worthless person?	better than usual / same as usual
23. Felt that life is entirely hopeless?	better than usual / same as usual
24. Felt that life isn't worth living?	better than usual / same as usual
25. Though of the possibility that you might make away with yourself?	better than usual / same as usual
26. Found at times you couldn't do anything because your nerves were too bad?	better than usual / same as usual
27. Found yourself wishing you were dead and away from it all?	better than usual / same as usual
28. Found that the idea of taking your own life kept coming into your mind?	better than usual / same as usual

Table 2.3 The General Health Questionnaire in Japanese [40]

質問項目	Score
Subscale (A) Somatic	
1. 気分は爽快ですか？	全くない–ない–たびたびある–ある
2. 疲労回復剤を飲みたいと思ったことはありますか？	全くない–ない–たびたびある–ある
3. 何となく疲れやすいですか？	全くない–ない–たびたびある–ある
4. 病気だと感じたことはありますか？	全くない–ない–たびたびある–ある
5. 病気だと感じたことはありますか？	全くない–ない–たびたびある–ある
6. 頭が重いように感じたことはありますか？	全くない–ない–たびたびある–ある
7. のぼせたり寒気がしたことはありますか？	全くない–ない–たびたびある–ある
Subscale (B) Anxiety and Insomnia	
8. 心配ごとがあってよく眠れないことはありますか？	全くない–ない–たびたびある–ある
9. 夜中に目を覚ますことはありますか？	全くない–ない–たびたびある–ある
10. 夜中に目を覚ますことはありますか？	全くない–ない–たびたびある–ある
11. イライラして怒りっぽくなったことがありますか？	全くない–ない–たびたびある–ある
12. 理由もなく，何かにおびえたり取り乱したりすることはありますか？	全くない–ない–たびたびある–ある
13. いろいろなことに重荷を感じたことはありますか？	全くない–ない–たびたびある–ある
14. 落ち着かずにじっとしていられないことはありますか？	全くない–ない–たびたびある–ある
Subscale(C) Social dysfunction	
15. 忙しく活動的な生活を送っていますか？	全くない–ない–たびたびある–ある
16. なんでもおっくうがらずにやれますか？	全くない–ない–たびたびある–ある
17. すべてがうまくいっていると感じることはありますか？	全くない–ない–たびたびある–ある
18. 毎日の仕事に満足していますか？	全くない–ない–たびたびある–ある
19. 自分のしていることにいきがいを感じることはありますか？	全くない–ない–たびたびある–ある
20. たやすく決断できますか？	全くない–ない–たびたびある–ある
21. 日常生活を楽しく送っていますか？	全くない–ない–たびたびある–ある
Subscale (D) Severe depression	
22. 自分は役に立たない人間だと考えたことはありますか？	全くない–ない–たびたびある–ある
23. 生きる望みをまったく失ったと感じたことがありますか？	全くない–ない–たびたびある–ある
24. 生きていることに意味がないと感じたことがありますか？	全くない–ない–たびたびある–ある
25. 自分なんてこの世にいない方がいいと感じたことはありますか？	全くない–ない–たびたびある–ある
26. ひどいノイローゼ状態を感じたことはありますか？	全くない–ない–たびたびある–ある
27. 死んだ方がマシだと感じたことはありますか？	全くない–ない–たびたびある–ある
28. 自殺しようと考えたことはありますか？	全くない–ない–たびたびある–ある

Table 2.4 State−Trait Anxiety Inventory [42]

Questionnaire	Score			
STAI Form Y-1				
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I feel tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self−confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I feel jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4
STAI Form Y-2				
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am “calm, cool, and collected”	1	2	3	4
28. I feel that difficulties are piling up so that I cannot over come them	1	2	3	4
29. I worry too much over something that really doesn’t matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self−confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can’t put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent and concerns and interests	1	2	3	4

1: Not at all, 2: Somewhat, 3: Moderately so, 4: Very much so

Table 2.5 State−Trait Anxiety Inventory in Japanese

Questionnaire	Score
STAI Form Y-1	
1. おだやかな気持ちだ	1 2 3 4
2. 安心している	1 2 3 4
3. 緊張している	1 2 3 4
4. ストレスを感じている	1 2 3 4
5. 気楽である	1 2 3 4
6. 気が動転している	1 2 3 4
7. なにかよくないことがおこるのではないかと心配している	1 2 3 4
8. 満足している	1 2 3 4
9. おびえている	1 2 3 4
10. 快適である	1 2 3 4
11. 自信がある	1 2 3 4
12. 神経過敏になっている	1 2 3 4
13. いらいらしている	1 2 3 4
14. ためらっている	1 2 3 4
15. くつろいでいる	1 2 3 4
16. 満ち足りた気分だ	1 2 3 4
17. 悩みがある	1 2 3 4
18. まごついている	1 2 3 4
19. 安定した気分だ	1 2 3 4
20. 楽しい気分だ	1 2 3 4
STAI Form Y-2	
21. 楽しい気分になる	1 2 3 4
22. 神経質で落ちつかない	1 2 3 4
23. 自分に満足している	1 2 3 4
24. とりのこされたように感じる	1 2 3 4
25. 気が休まっている	1 2 3 4
26. 冷静で落ちついている	1 2 3 4
27. 困ったことが次々におこり克服できないと感じる	1 2 3 4
28. 本当は大したことではないものに心配しすぎる	1 2 3 4
29. しあわせだと感じる	1 2 3 4
30. いろいろ頭にうかんできて仕事や勉強が手につかない	1 2 3 4
31. 自信がない	1 2 3 4
32. 安心感がある	1 2 3 4
33. すぐにものごとを決めることができる	1 2 3 4
34. 力不足を感じる	1 2 3 4
35. 心が満ち足りている	1 2 3 4
36. つまらないことが頭にうかび悩まされる	1 2 3 4
37. ひどく失望するとそれが頭から離れない	1 2 3 4
38. 落ちついた人間だ	1 2 3 4
39. 気になることを考え出すと緊張したり混乱したりする	1 2 3 4
40. 嬉しい気分になる	1 2 3 4

1: ほとんどない, 2: ときどきある, 3: たびたびある, 4: ほとんどいつも

2.3 Results

2.3.1 Demographic characteristics

The demographic, clinical, and laboratory characteristics of all subjects are shown in Table 2.6. The mean age in the control group was significantly higher than those in the DM and non−DM groups.

2.3.2 Frequency−domain measures

Figures 2.6 and 2.7 show examples of original photoplethysmography waveforms and P−P intervals, respectively, in the part of study session. Figure 2.8 shows examples of power spectrum density for: (a)–(b), healthy adults; (c)–(d), DM patients; and (e)–(f), non−DM patients. Figure 2.9 shows the mean values of the power spectra. There were no significant differences among the groups. However, the HF spectrum after starting hemodialysis was larger in the DM group than in the other groups, and LF/HF after starting hemodialysis was smaller in the DM group than in the other groups.

2.3.3 Fractal scaling measures

Figure 2.10 shows the results of DFA. The mean α_1 after starting the hemodialysis session was significantly smaller in DM patients than in healthy adults or non−DM patients, and also significantly smaller than the mean α_1 in DM patients before starting the hemodialysis session. There was no significant difference among the groups with regard to α_2.

2.3.4 Crossover phenomena

As shown in Table 2.7, α_1/α_2 was less than zero only in the DM group after starting hemodialysis. These results suggest that reverse crossover phenomena and deviation from the fluctuation rhythm with $1/f$ occur in the autonomic nervous system of DM patients after starting a hemodialysis session.

Table 2.6 Demographic, clinical and laboratory characteristics of all subjects

	Control	DM	non-DM	*P*
Number of patients (man / woman)	14 (7/7)	7 (6/1)	7 (5/2)	
Age (year)	34.32 ± 3.30 **	64.12 ± 12.78	69.65 ± 10.83	N.S.
Duration of HD (year)	−	4.12 ± 8.56	3.67 ± 9.49	N.S.
Hight (m)	−	161.9 ± 11.8	160.1 ± 8.1	.37
BMI	−	22.6 ± 4.7	21.7 ± 2.2	.33
Dry Wight (Kg)	−	59.3 ± 12.7	56.1 ± 10.9	.31
HD time (hr)	−	4.1 ± 0.4	4.0 ± 0.0	.18
Interdialytic weight gain (Kg)	−	3.4 ± 0.5	3.1 ± 1.1	.20
Interdialytic weight gain (%body weight)	−	6.04 ± 1.47	5.44 ± 1.56	.24
Ultrafiltration volume (L)	−	3.6 ± 0.4	3.2 ± 0.8	.11
Remove body fluid (%body weight)	−	6.3 ± 1.5	5.7 ± 1.1	.19
Ultrafiltration rate (ml/h)	−	854.3 ± 74.1	777.1 ± 182.9	.17
Blood flow during dialysis (ml/min)	−	208.6 ± 15.7	222.9 ± 18.0	.07
Serum albumin concentration (g/dl)	−	3.7 ± 0.3	3.9 ± 0.2	.08
Serum sodium concentration (mEq/L)	−	136.9 ± 5.3	140.1 ± 1.21	.08
Serum chloride concentration (mEq/L)	−	103.9 ± 5.3	99.6 ± 18.5	.29
Serum potassium concentration (mEq/L)	−	4.8 ± 0.6	4.9 ± 0.5	.37
Serum calcium concentration (mEq/L)	−	8.7 ± 0.6	8.8 ± 0.6	.40
Serum phosphorus concentration (mEq/L)	−	4.7 ± 1.0	5.0 ± 1.3	.29
blood urea nitrogen (mg/dl)	−	57.1 ± 11.0	60.6 ± 6.6	.24
uric acid (mg/dl)	−	8.1 ± 2.0	8.7 ± 2.6	.32
Serum creatinine concentration (g/dl)	−	9.9 ± 3.1	10.6 ± 2.5	.33
LDL-C (mg/dl)	−	71.4 ± 23.2	173.4 ± 25.9	.25
HDL-C (mg/dl)	−	38.9 ± 16.4	49.3 ± 8.7	.09
LDH (IU/L)	−	202.3 ± 46.3	173.4 ± 25.9	.09
CK (IU/L)	−	84.0 ± 57.7	73.9 ± 29.7	.34
ChE (IU/L)	−	237.9 ± 49.3	212.7 ± 51.7	.19
TP (g/dl)	−	6.5 ± 0.4	6.3 ± 0.4	.13
Hb (g/dl)	−	11.0 ± 0.9	10.7 ± 0.7	.29
Hematocrit (%)	−	33.3 ± 3.3	33.3 ± 2.2	.05
hANP (pg/ml)	−	79.2 ± 69.9	108.9 ± 132.0	.32
PCR (g/Kg/day)	−	0.8 ± 0.2	0.9 ± 0.1	.21
Kt/V	−	1.43 ± 0.28	1.64 ± 0.25	.09

Results reported as mean ± standard deviation. Differences among the three groups were assessed by the Kruskal−Wallis test; if $P<0.05$, between–group comparisons were performed with the Mann–Whitney *U*–test.
Abbreviations: LDL−C, low–density lipoprotein cholesterol; HDL−C, high–density lipoprotein cholesterol; LDH, lactate dehydrogenase; CK, creatine kinase; TP, total protein; Hb, hemoglobin concentration; hANP, human atrial natriuretic peptide; PCR, protein catabolic rate. ** $P < 0.01$.

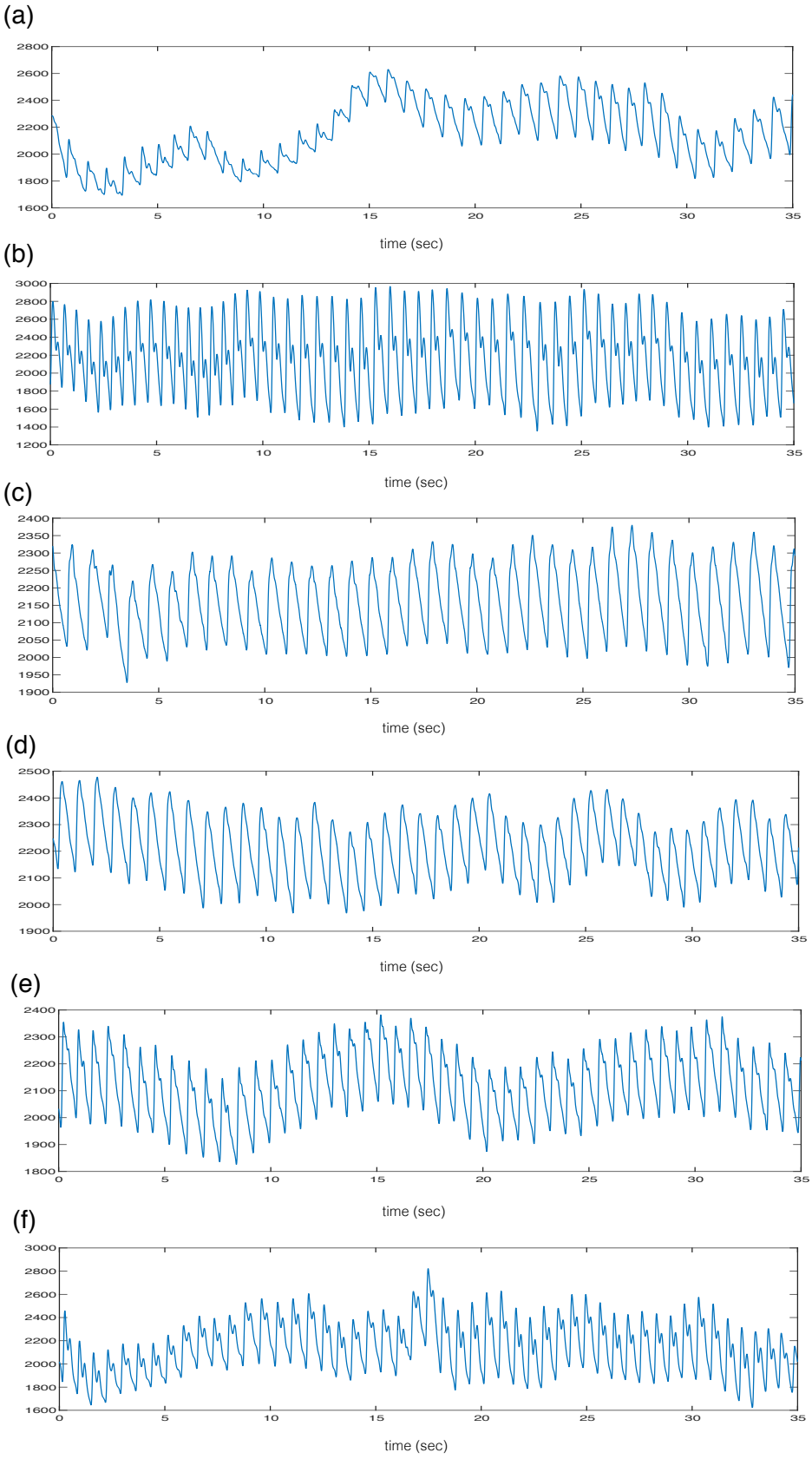

Figure 2.6 Examples of original waveform of photoplethysmography

Photoplethysmography waveform for: (a)–(b), healthy adults; (c)–(d), DM patients; and (e)–(f), non–DM patients.

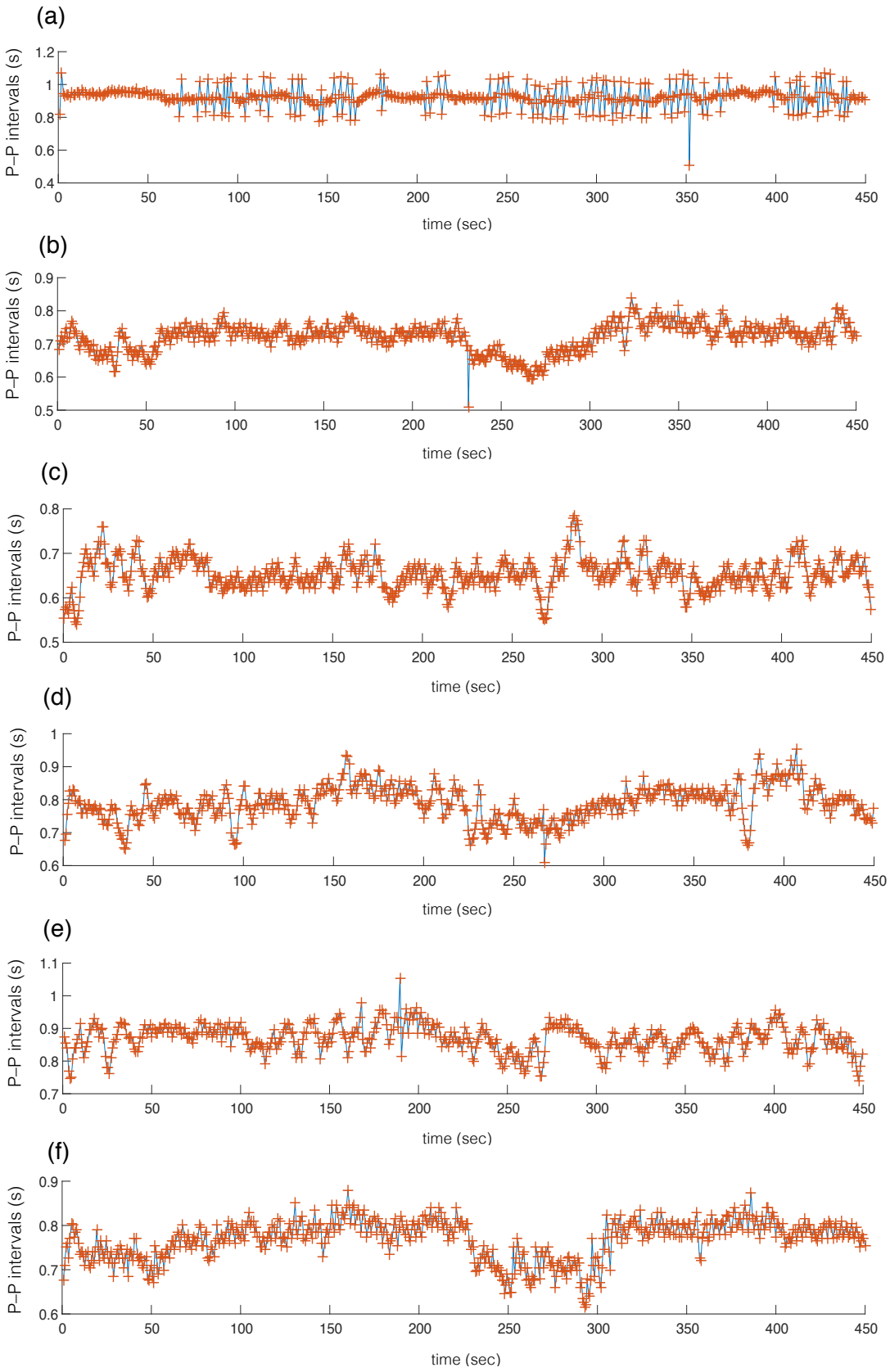

Figure 2.7 Examples of P−P intervals in of photoplethysmography data

P−P intervals for: (a)–(b), healthy adults; (c)–(d), DM patients; and (e)–(f), non–DM patients.

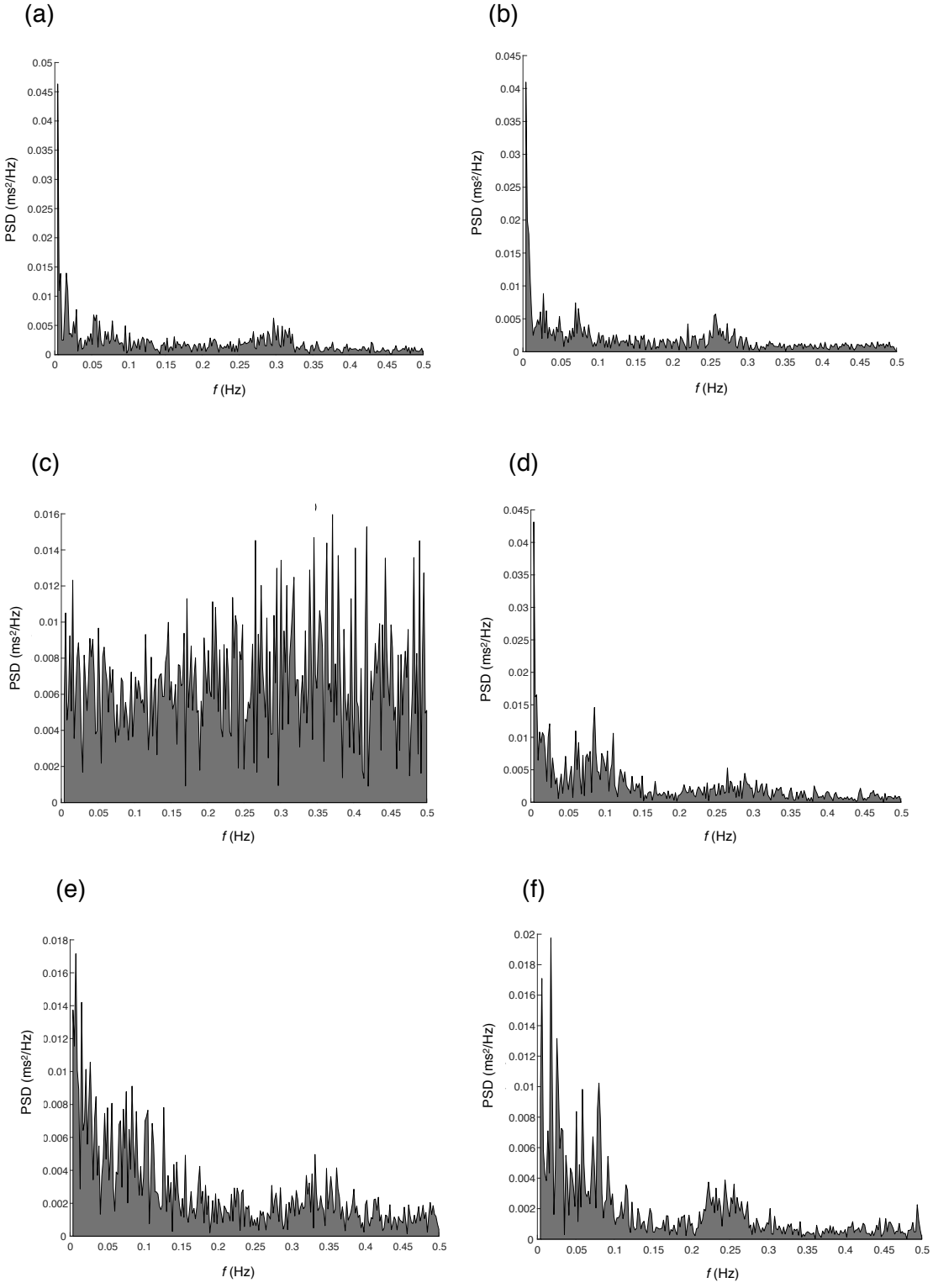

Figure 2.8 Examples of power spectrum density in P−P intervals of photoplethysmography data during hemodialysis session

Power spectrum density for: (a)–(b), healthy adults; (c)–(d), DM patients; and (e)–(f), non–DM patients.

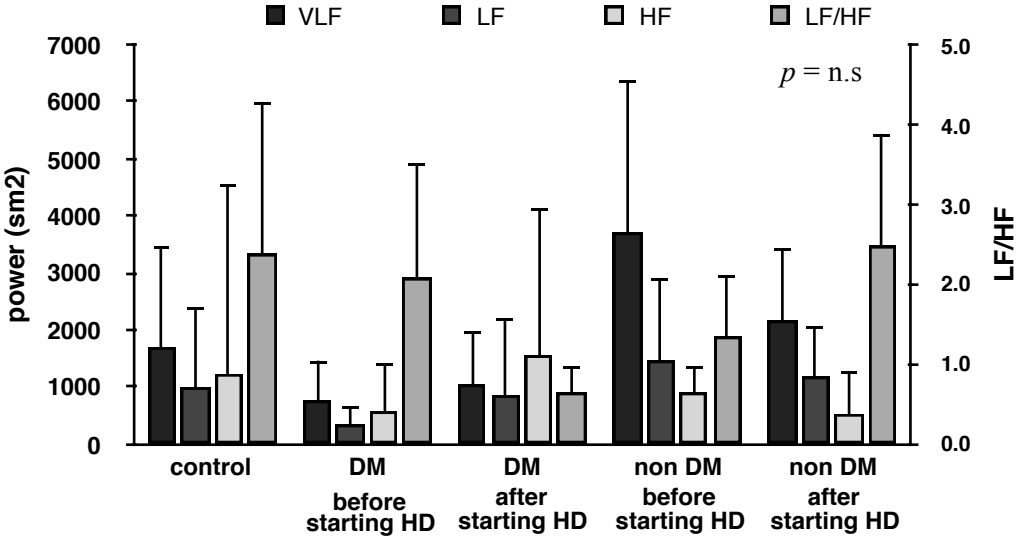

Figure 2.9 Power spectra of P−P intervals in VLF, LF, HF and LF/HF

Data are shown as mean ± standard deviation.

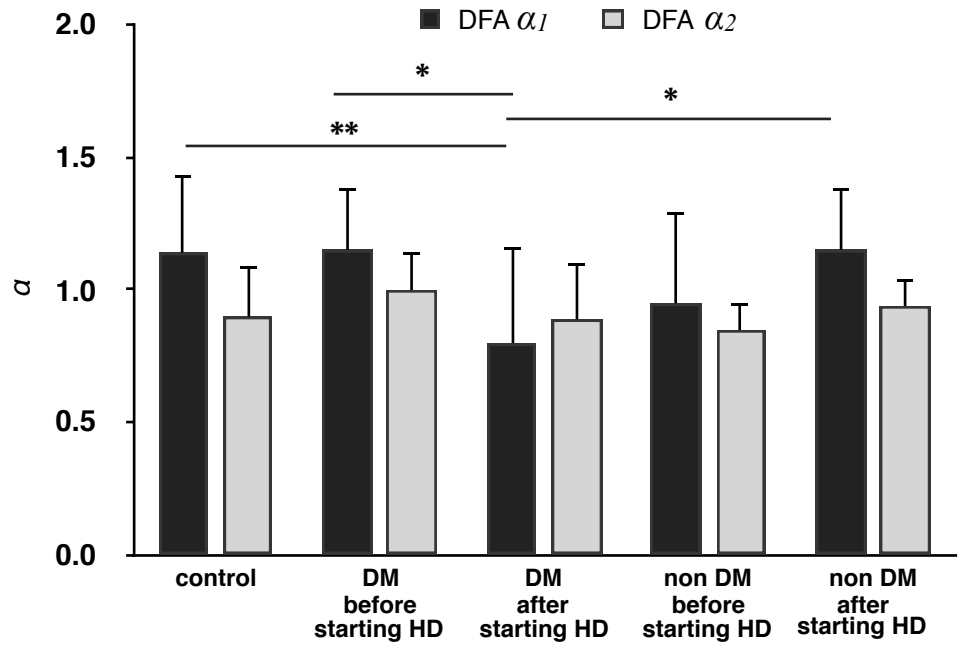

Figure 2.10 Comparison of scaling exponent α_1 in control and hemodialysis patients.

Data are shown as mean ± standard deviation.
** $P < 0.01$, * $P < 0.05$.

Table 2.7 α_1, α_2, and α_1/α_2 in hemodialysis patients and healthy adults

Subjects		α_1	α_2	α_1/α_2
control		1.14 ± 0.29	0.89 ± 0.19	1.28 ± 1.53
DM	before starting HD	1.15 ± 0.27	0.99 ± 0.14	1.16 ± 1.93
	after starting HD	0.79 ± 0.36	0.88 ± 0.22	**0.90 ± 1.64**
non–DM	before starting HD	0.94 ± 0.34	0.80 ± 0.11	1.18 ± 3.09
	after starting HD	1.01 ± 0.23	0.94 ± 0.09	1.07 ± 2.56

Data are shown as mean ± standard deviation. α_1/α_2 of the after starting hemodialysis in the DM only showed less than 1.0.

2.3.5 GHQ−28

Figure 2.11 (a)−(d) shows the results of the GHQ−28 evaluation. The somatic symptom scores (subscale A) were as follows: control = 3.0 (3.0–2.0), DM = 4.0 (5.5–2.0), and non−DM = 2.0 (2.0−2.0). The somatic symptom scores in the DM group tended to be higher than those in the non−DM group ($P < 0.1$). The scores for anxiety and insomnia (subscale B) were as follows: control = 2.5 (3.0–1.0), DM = 2.0 (2.5–1.5), and non−DM = 1.0 (2.5–1.0). There were no significant differences among the groups. The scores for social dysfunction (subscale C) were as follows: control = 2.0 (2.0–1.3), DM = 2.0 (2.5–1.5), and non−DM = 1.0 (1.5–1.0). There was no significant difference among the control, DM, and non−DM groups. The scores for severe depression (subscale D) were as follows: control = 1.0 (1.0–0.3), DM = 2.0 (2.5–2.0), and non−DM = 1.0 (1.5–1.0). The score for severe depression was significantly higher in the DM group than in the control group ($P<0.05$).

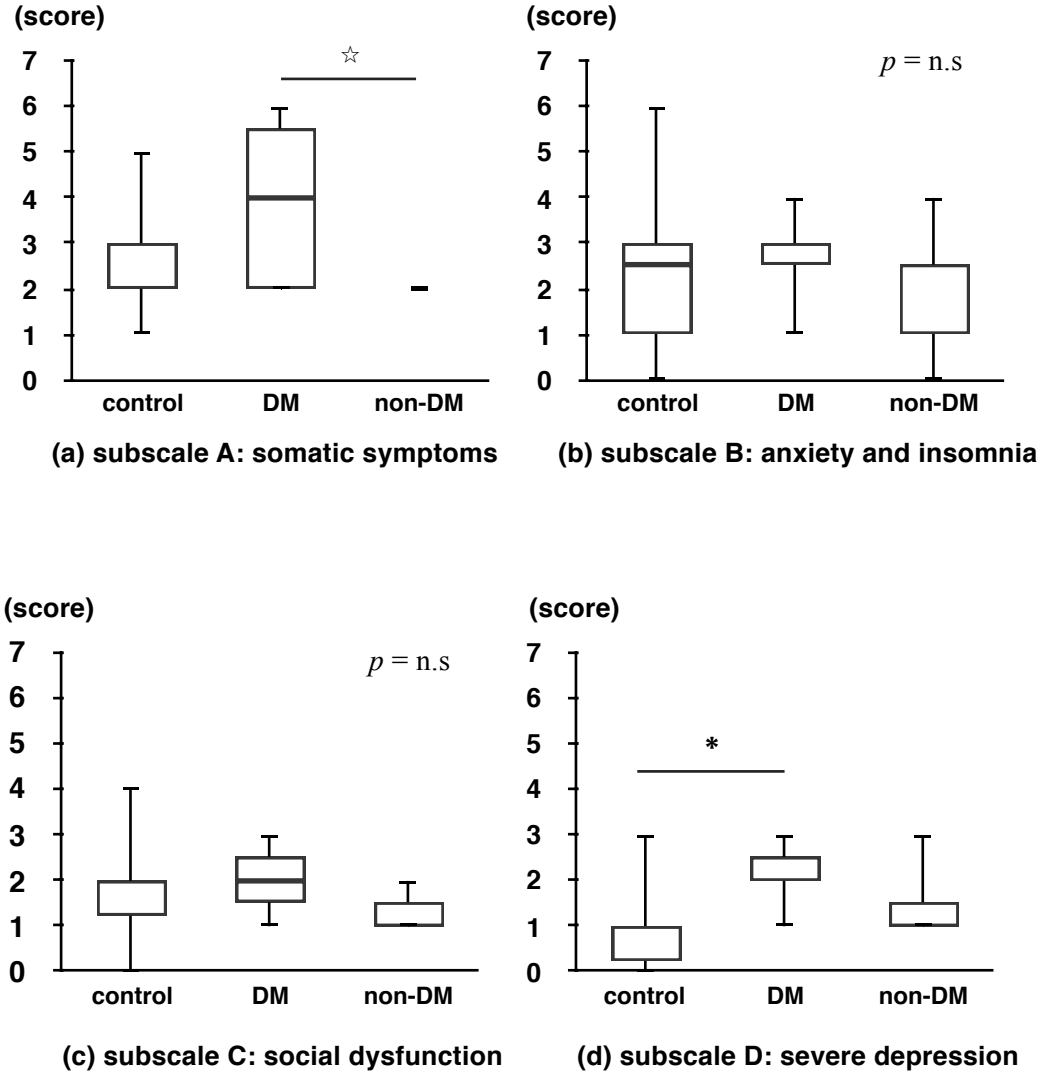

Figure 2.11 Comparison of the GHQ−28 scores between dialysis patients with diabetes and those without diabetes.

HD: hemodialysis, DM: diabetic nephropathy patients, non−DM: non−diabetic nephropathy patients.
The horizontal bar within the box corresponds to the median. The upper and lower bars of the boxes correspond to the first and third quartiles, respectively. The two vertical lines outside the box extend to the smallest and largest observations. The asterisk indicates the significant difference between each group. The star indicates the tendency between groups. $*P < 0.05$, $☆P < 0.1$.

2.3.6 STAI

The STAI scores for state anxiety were as follows: control = 2.0 (1.25–2.75), DM = 3.0 (3.0–2.0), and non–DM = 2.0 (1.0–2.0). There was no significant difference among the groups. The STAI scores for trait anxiety were as follows: control = 1.0 (1.0–2.0), DM = 3.0 (2.0–3.5), and non–DM = 2.0 (1.5–3.0). Neither state nor trait anxiety scores significantly differed among the control, DM, and non–DM groups.

2.4 Discussion

2.4.1 Autonomic nervous activity

In this study, I evaluated autonomic nervous responses before and after starting hemodialysis in patients with diabetic nephropathy and non−diabetic nephropathy, by detecting the photoplethysmography P−P interval. The results of this study suggest that diabetic nephropathy patients demonstrate an imbalance of autonomic function after starting hemodialysis, as indicated by a low α_1 value. This phenomenon could be the result of metabolic changes triggered by starting hemodialysis. As the movement of blood from vessel to blood circuits progresses upon starting hemodialysis, a blood pressure drop is induced because of decreasing circulating plasma volume. However, various compensatory mechanisms function to prevent hypotension in the human body. Baroreceptors, sensors that act as compensatory regulators, and the sympathetic nervous system increase heart rate by enhancing cardiac contractions, upon sensing a decrease in blood pressure. Furthermore, the vascular resistance and capacitance of vessels prevent a sudden drop in blood pressure, allowing normal circulation to be maintained [44–45]. The main reason for the decrease in blood pressure during hemodialysis is the decrease in the volume of circulating plasma. Dysfunction of the autonomic nervous system causes poor reflection in the contraction of the vessels. Consequently, this event causes a rapid decrease in blood pressure. When the posture of a diabetic patient changes rapidly, the hemodynamic response cannot respond adequately [46]. The malfunction of blood pressure autoregulation has been noted in long−term diabetes patients [47]. With the repositioning and excessive disability suddenly imposed on diabetic patients by hemodialysis, they may be unable to respond to rapid changes in hemodynamics. A lack of cardiovascular reflection can also lead to potentially lethal arrhythmia and sudden death [48–50].

The heart beat rhythm is determined by antagonism of the sympathetic and parasympathetic nervous system. Relative suppression of sympathetic nervous system activity has little effect on the scaling exponent reflecting the influence of autonomic nervous activity on the scaling of HRV. Therefore, my result can be considered to indicate that the relative suppression of the parasympathetic nervous system causes the value of the scaling exponent to approach Brownian noise in the form of the reverse crossover phenomenon.

2.4.2 Psychological tests

Many hemodialysis patients have psychological problems because they are subjected to many stresses such as emotional and social challenges. Therefore, it is necessary to assess the mental and physical state of hemodialysis patients with a multifaceted evaluation incorporating both physiological and psychological viewpoints. However, evaluation of the mental and physical state is challenging, because no objective and reproducible measurement has been established to evaluate these factors sufficiently. Moreover, the process is difficult to ascertain because the development of mental health issues is highly individual. When a mental health problem occurs, it does not necessarily appear as a psychological symptom. Instead, a physical symptom, mainly related to the autonomic nervous system such as headache, sleeplessness, fatigue, or gastrointestinal disruption, may often emerge. ESKD patients must undergo dialysis two or three times per week. Thus, hemodialysis creates temporal, social, and economic limitations. Some hemodialysis patients have deep concern for their future income and employment. Many patients with hemodialysis and their families are worried about the progression of kidney disease to more serious diseases or complications such as kidney cancer, movement disorder, or dementia. These worries could undesirably influence hemodialysis patients both physically and mentally.

In this study, the Japanese version of the GHQ−28 was used to assess patients' mental health status. My data confirm the tendency for diabetic nephropathy patients to be depressed. Depression is a serious and common psychiatric disorder. Diabetes imposes restrictions on daily life and leads to physical pain, despair, and signs of uneasiness such as tension and sleeplessness. These events could be risk factors for depression.

The STAI has been used extensively in research and clinical practice. It consists of separate self−report scales to measure state and trait anxiety. STAI results did not significantly differ between diabetic nephropathy patients and non−diabetic nephropathy patients. These results indicate that there is no difference in the psychological state of anxiety between these patient populations. Psychological changes immediately before and after starting hemodialysis did not appear to affect autonomic nervous activity dynamics. Hemodialysis patients tend to show signs of mental and emotional distress such as anxiety and depression in many situations due to a sense of loss in life. In this study, psychological problems were observed in patients with diabetic nephropathy. The possibility that abnormalities in autonomic nervous function were enhanced by psychological and emotional factors was also considered.

2.5 Conclusion

I examined whether or not extracorporeal circulation influences autonomic nervous system function in patients with CKD by photoplethysmogram recording in conjunction with the evaluation of psychosomatic symptoms and anxiety states using the General Health Questionnaire (GHQ–28) and the State–Trait Anxiety Inventory (STAI), respectively, to investigate the relationship between autonomic nervous activity and anxiety state. Autonomic nervous function in patients with diabetic nephropathy is presumed not to react robustly to external factors, in part because of decreased sympathetic activity and increased parasympathetic activity. Indicators of poor cardiovascular reflexes such as hypotension may be caused by imbalance between the sympathetic and parasympathetic nervous system in patients with diabetic nephropathy.

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Conflict of interest: The author declares no competing financial interests.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Yodogawa Christian Hospital.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Chapter III

Autonomic Nervous Activity in High Ultrafiltration Rate

3.1 Introduction

Cardiovascular diseases are the leading cause of the death in patients with end stage kidney diseases (ESKD). Hypertension plays a major role in cardiovascular diseases, and patients with ESKD require strict control of intake volume. A survey by the Japanese Society for Dialysis Therapy (JSDT) suggested that a >6% weight loss between two consecutive hemodialysis (HD) sessions was associated with to a significant increase in risk of death [51]. Since, as an ultrafiltration rate (UFR) of 15 ml/hr/kg is equal to the removal of 6% of body weight as water in 4 hours, the average UFR would be ≤15 ml/hr/kg. Moreover, higher UFR was shown to be independently associated with patient mortality [52]. Intradialytic hypotension is a critical complication and an independent risk factor for mortality in patients on hemodialysis [53]. The main causes of intradialytic hypotension have been reported that the initiating factor in the pathogenesis of intradialytic hypotension is a decrease in blood volume. The decrease of blood volume is the consequence of the capillary starling equilibrium, which determines the refilling rate. Many factors influence the refilling rate. As a result, it is difficult to predict the changes of blood volume during dialysis [54]. During HD treatment, blood pressure usually decreases with body weight loss, with the reduction in blood pressure mainly due to a reduction in circulating plasma volume (Figure 3.1–3.2). As plasma volume decreases, the baroreceptor reflex acts as a compensatory mechanism, stimulating the sympathetic nervous system, enhancing cardiac contraction, and increasing heart rate and blood pressure. The vascular resistance and capacitance of blood vessels prevent a sudden drop in blood pressure, allowing normal circulation to be maintained [44−45, 55].

In some patients, intradialytic blood pressure during HD does not necessarily depend on ultrafiltration volume. Increasing sympathetic activity as a compensatory mechanism may increase heart rate or cardiac output, resulting in elevated blood pressure. Sympathetic overactivity, however, may have negative effects on circulation dynamics, resulting in myocardial ischemia, life–threatening arrhythmia with tachycardia, and clot formation with increased platelet adhesiveness. Assessment of autonomic nervous activity during HD may reduce the risk of cardiovascular complications in these patients.

Analysis of time and frequency domain measures of heart rate variability (HRV) from Holter ECG recordings is an accepted and noninvasive method of assessing autonomic nervous system activity. As instantaneous heart rate depends on the

interaction between sympathetic and parasympathetic nervous activity, HRV analysis may lead to quantification of autonomic regulation of heart rate. Frequency domain analysis is a fractional determination method that differentiates activity of the sympathetic and parasympathetic nerves from R−R interval dynamics [56–58]. HRV analysis is widely utilized as an index of cardiac autonomic dysfunction and modulation. In previous studies, measurements of autonomic nervous function during HD were accompanied by variations in blood pressure. Intradialytic hypertension in a significant proportion of patients is due to sympathetic overactivity with feed–forward blood pressure enhancement [46, 59]. The complex characteristics of HRV can also be analyzed quantitatively by methods that include the Lyapunov exponent, sample entropy, approximate entropy (ApEn) and 1/*f* fluctuation. In particular, ApEn can quantify the degree of complexity over time [60], with higher ApEn indicating greater irregularity and lower ApEn indicating more regularity. Although that trial included subjects with variable blood pressure, subject losses during follow up after HD were expected.

Clinical studies have shown that excessive UFR (12.37 ml/h/kg body weight) in patients on regular thrice weekly HD treatment is independently associated with an increased long–term risk of death [61]. However, the clear evidence to determine the appropriate UFR was not yet exist at present. Moreover, decreased HRV have been shown to be a risk factor for mortality in hemodialysis patients [62]. To my knowledge, however, there are few reports about the most suitable UFR based on changes in autonomic nervous activity in subjects without blood pressure variation. This study therefore assessed the most suitable UFR range from point of the autonomic nervous system function by power spectral analysis of R−R interval dynamics in UFR subjects without blood pressure variation.

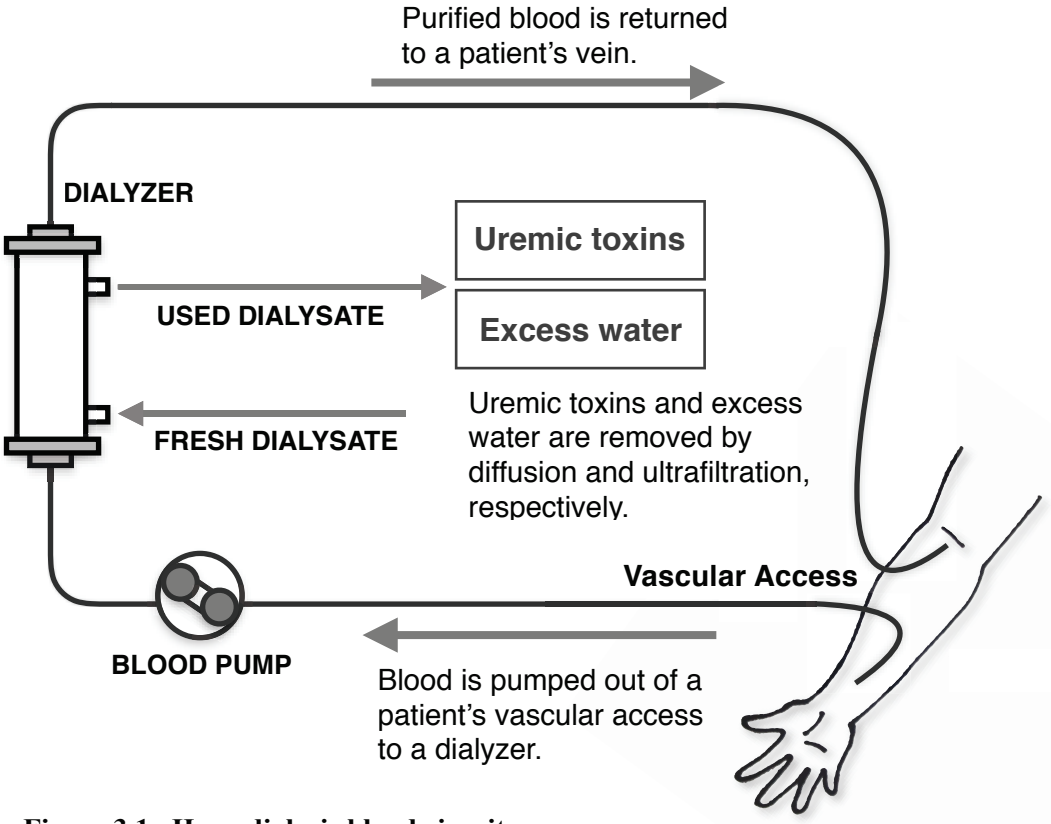


Figure 3.1 Hemodialysis blood circuit

Blood from a vascular access is pumped into dialyzer through the blood line. The wast products such as uremic toxins or excess water are removed through a dialyzer by diffusion and ultrafiltration.

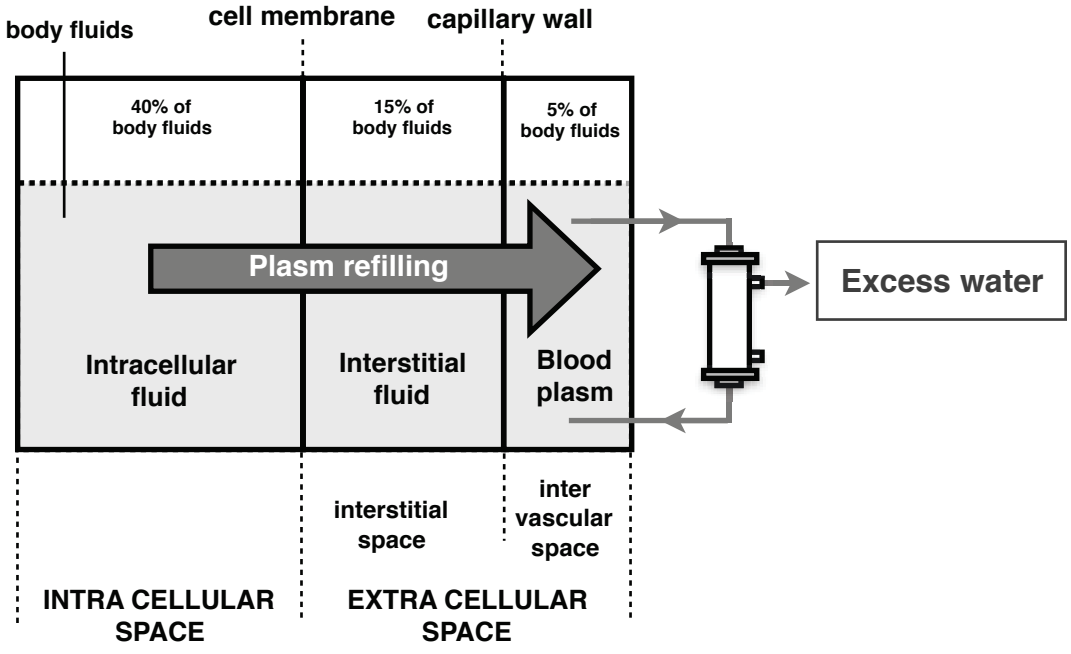


Figure 3.2 Schematic diagram of plasma refilling in three compartment model

The excess water was removed directly from inter vascular space which is refilled with fluid from the inter cellular space and interstitial space.

3.2 Methods

3.2.1 Subjects

Forty−three end−stage kidney disease (ESKD) patients undergoing HD were enrolled in this study. Patients with chronic atrial fibrillation, frequent ventricular premature beats, a permanent pacemaker, taking antihypertensive drugs (amezinium metilsulfate or droxidopa) before and during the HD session were excluded from this study. The patients were monitored blood pressure during a HD session. Intradialytic hypotensive or hypertensive episodes defined as a period of at least 20 mmHg decrease or increase in systolic blood pressure between the beginning and the end of a HD session, respectively. In our study, intradialytic hypotensive episodes (n = 8) were occurred and excluded from the study. Hence, the study subjects consisted of 35 patients undergoing HD. Patients underwent dialysis for 4 hours three times per week in Yodogawa Christian Hospital, using a polysulfone (APS−SA® or MD® series; Asahikasei Medical, Tokyo, Japan) or cellulose triacetate (FB−U® series; Nipro, Osaka, Japan) membrane dialyzer. The UFR during each HD session was liner and adapted to reach the dry weight (DW). The DW was determined on clinical grounds, and reflects the lowest weight the patient can tolerate without intradialytic symptoms and hypotension in the absence of overt fluid overload. The DW was not necessarily stable over an extended period of time before study entry because the DW was modified by the attending doctor as needed. The sodium, chloride, potassium, calcium, magnesium, and acetic acid bicarbonate concentrations of the dialysate solution were 140, 112.25, 2.0, 2.75, 1.0, 8, and 27.5 mEq/l, respectively, and the glucose concentration was 125 mg/dl. The temperature of the dialysate solution was maintained at 35.5 to 36.0°C. Blood flow rates ranged from 180 to 240 ml/min, and the dialysate solution flow rate was 500 ml/min. The subjects were divided into 3 groups based on the volume of UFR during an HD session, patients with UFR < 10 ml/hr/kg (Group I, n=14); ≥10 ml/hr/kg but ≤ 15 ml/hr/kg (Group II, n=10); and >15 ml/hr/kg (Group III, n=11). All subjects provided informed consent, and the study protocol was approved by the Ethics Committee of the Yodogawa Christian Hospital.

3.2.2 Blood pressure and heart rate

Blood pressure and heart rate were measured every 30 minutes during HD, beginning 15 minutes before starting and 15 minutes after ending each HD session (Figure 3.3). Blood pressure was measured with an automatic sphygmomanometer. The cuff band was wrapped around the upper arm contralateral to the location of vascular access. The subject was instructed to keep resting in a supine position.

3.2.3 Holter ECG

Electrodes (leads II and CM5) were placed on each patient's chest before starting the HD session, and Holter ECG (RAC−3203; Nihon Kohden, Tokyo, Japan) was recorded continuously, beginning 15 minutes before starting and 15 minutes after ending each HD session. Holter ECG data were collected at a sampling rate of 1000 Hz and transferred to the automatic electrocardiogram analysis apparatus (DSC−3200, Nihon Kohden, Tokyo, Japan), with all QRS complexes detected automatically. The results of each automatic analysis were reviewed, and any errors in QRS detection or frequent ventricular and supraventricular ectopic beats were removed manually, with removed R−R intervals replaced by conventional spline interpolation.

3.2.4 Heart rate variability

R−R intervals of ECG in the frequency domain were analyzed to determine HRV. The edited data were preprocessed to exclude artifacts by eliminating R−R intervals greater than R−Rave ± 3σ. Data were analyzed with Kubios HRV Analysis Software 2.0 (Biomedical Imaging Analysis Group, Department of Applied Physics, University of Kuopio, Finland) [63]. Spectral analysis of HRV was performed every 30 minutes using Welch's and autoregressive methods. Power spectral densities within the very low frequency (VLF: 0.003–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), and high frequency (HF: 0.15–0.4 Hz) component bandwidths were determined [15], with all frequency domain components expressed in absolute units (ms^2) (Table 3.1). LF and HF power were normalized to distinguish between the effects of sympathovagal balance and VLF.

Normalized low frequency power (LFnorm) was calculated as LF divided by total frequency (TF) power–VLF.

$$\text{LFnorm} = \frac{LF}{Total\ \ power - VLF} \times 100 \tag{3.1}$$

Normalized high frequency power (HFnorm) as HF over TF power–VLF.

$$\text{HFnorm} = \frac{HF}{Total\ \ power - VLF} \times 100 \tag{3.2}$$

LF represented sympathetic activity, and HF represented parasympathetic activity. The ratio of LFnorm to HFnorm (LF/HF), representing the balance between sympathetic and parasympathetic activity, was calculated [15].

Table 3.1 Frequency domain parameters (Summarized from [15]).

Variable	Units	Description	Frequency range
Total power	ms^2	Variance of all R−R intervals	approximately ≤ 0·4 Hz
VLF	ms^2	Power in very low frequency range	0.003–0.04 Hz
LF	ms^2	Power in low frequency range	0.04–0.15 Hz
LF norm	n.u.	LF power in normalised units	
HF	ms^2	Power in high frequency range	0.15–0.4 Hz
HF norm	n.u.	HF power in normalised units	
LF/HF ratio	n.u.	ratio LF [m^2]/ HF [m^2] frequency	

3.2.5 Approximate entropy

ApEn measures the complexity or irregularity of the signal. ApEn is associated with increased or decreased activity of autonomic nervous system. Nonlinear methods of heart rate analysis provide information about the dynamics of heart rate, and are widely used to determine the status of the autonomic nervous system [64]. Large values of ApEn indicate high irregularity and smaller values of ApEn indicate a more regular signal. ApEn also determines the probability of finding specific patterns in the time series [65]. In calculating ApEn, first, a set of length m vectors u_j is constructed from the original time series (R−R intervals in this study) .

$$C_j^m(r) = \frac{number\ of\left\{u_k \middle| d(u_j, u_k) \le r\right\}}{N-m+1} \forall\ k. \tag{3.3}$$

Where m is the embedding dimension and N is the number of measured R−R intervals. The distance of the vectors is determined as a maximal distance d of the corresponding components in the vector.

$$u_j = \left(RR_j, RR_{j+1}, \ldots, RR_{j+m-1}\right),\ \ j = 1, 2, \ldots N-m+1 \tag{3.4}$$

For each u_j the relative number of vectors u_k is for which $d(u_j, u_k) \le r$ is calculated. This index is denoted as

$$d\left(u_j, u_k\right) = \max\left\{\left| RR_{j+n} - RR_{k+n} \right| n = 0, \ldots, m-1\right\}. \tag{3.5}$$

Finally, the approximate entropy is defined as

$$ApEn(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r). \tag{3.6}$$

ApEn depends on three parameters: *m*, defined as length of comparable runs; *r*, defined as the tolerance value; and *N*, defined as the length of time for the series [65]. As a common selection for ApEn, the variables were set at m = 2 and r = 20% of standard deviation of the time series.

3.2.6 Statistical analysis

Clinical characteristics of the three groups of dialysis patients were compared using the Kruskal–Wallis test; if this test yielded a *P* value <0.05, between group comparisons were assessed using the Mann–Whitney *U*–test. Blood pressure, heart rate, HF, LF/HF and ApEn were compared using Kruskal–Wallis tests, followed by post–hoc Dunn tests for each time series. All statistical analyses were performed using of JMP 10 software (SAS Institute, Inc), with a *P* value <0.05 considered statistically significant.

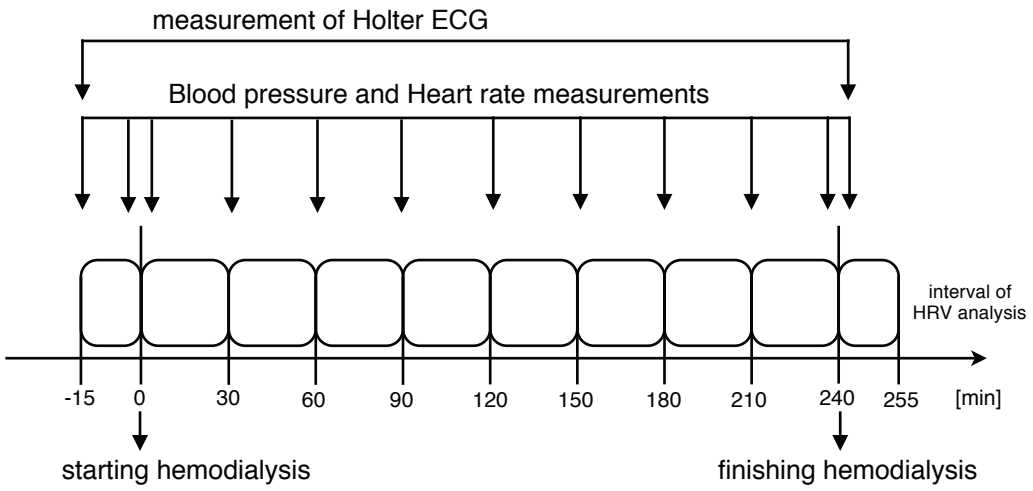


Figure 3.3 Experiment procedure for Holter ECG, blood pressure and heart rate measuring

Blood pressure and heart rate were measured every 30 minutes during HD.
Spectral analysis of HRV was performed every 30 minutes.

3.3 Results

3.3.1 Demographic characteristics

The demographic, clinical, and laboratory characteristics of all subjects are shown in Table 3.2. Interdialytic weight gain (%body weight gain), ultrafiltration volume and volume of body fluid removed were significantly higher in Group III than in the other two groups. UFR was also higher in Group III than in Groups I and II.

3.3.2 Blood pressure and heart rate

Figure 3.4 and 3.5 show the examples of R−R intervals of original ECG data and the examples power spectrum density in the prat of study session, respectively. Figure 3.6 shows changes in blood pressure in the three groups. Systolic and diastolic blood pressure at each time point remained constant in Groups I and II, beginning 15 min before starting HD until 15 min after the end of HD. In Group III, however, systolic blood pressure at the end of HD and 15 minutes later was significantly higher than before starting HD (P<0.05). Figures 3.7 shows changes in heart rate in the three groups. Heart rate in Group III tended to be higher 150 minutes after starting HD than before HD (P<0.1) and was significantly higher at all subsequent time points than before starting HD (P<0.05).

3.3.3 Frequency domain analysis

Figure 3.8 shows changes in HF in the three groups. HF remained constant in Groups I and II, from before starting HD (control) to after the end of HD. In Group III, however, HF at 90−120 minutes, 150−180 minutes, 180−210 minutes and after finishing HD was significantly lower than before starting HD (P<0.05 each). HF at 210−240 minutes was significantly lower than before starting HD (P<0.01), whereas HF at 120−150 minutes tended to be lower than before starting HD (P<0.1). Figures 3.9 shows changes in LF/HF in the three groups. LF/HF ratios also remained constant in Groups I and II, from before starting HD to after the end of HD. In group III, however, LF/HF ratios were significantly higher at 90−120, 150−180, and 210−240 minutes than before starting HD (P<0.05 each), and LF/HF ratios at 120−150 minutes

and after finishing HD tended to be higher than LF/HF before starting HD (P<0.1 each).

3.3.4 Approximate entropy

The results of ApEn are presented in Figure 3.10. Compared with ApEn before starting HD, ApEn values at all subsequent time points were unchanged in Groups I and II. In Group III, ApEn value at 120−150 minutes and at all subsequent time points were significantly higher than ApEn before starting HD (P<0.01 each).

TABLE 3.2 Clinical characteristics

	All Patients (N = 35)	Group I (N = 14)	Group II (N = 10)	Group III (N = 11)	*P*–value			
					K–W	I vs. II	I vs. III	II vs. III
Male / women	27 / 8	13 / 1	7 / 3	7 / 4	—			
Age (year)	67.08 ± 10.22	66.04 ± 12.44	66.46 ± 8.74	68.95 ± 8.91	0.835			
Duration of HD (year)	4.39 ± 4.25	4.73 ± 4.85	4.17 ± 4.44	2.76 ± 3.15	0.878			
Height (m)	160.8 ± 9.7	164.3 ± 6.0	156.6 ± 9.8	160.4 ± 12.3	0.541			
Body mass Index (kg/m^2)	21.5 ± 3.4	22.5 ± 3.8	22.1 ± 3.4	19.8 ± 2.6	0.165			
Dry weight (Kg)	55.8 ± 10.8	60.6 ± 10.2	54.3 ± 10.8	51.1 ± 9.9	0.430			
HD time (hr)	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	1.000			
Interdialytic weight gain (Kg)	2.9 ± 1.0	3.5 ± 0.8	2.8 ± 0.7	3.8 ± 0.8	< 0.0001 **	0.139	< 0.0001 **	0.111
Interdialytic weight gain (%body weight)	5.2 ± 1.8	4.8 ± 1.7	5.1 ± 0.4	7.3 ± 0.8	< 0.0001 **	0.060	< 0.0001 **	0.015 *
Ultrafiltration volume (L)	3.0 ± 0.9	2.5 ± 0.8	2.9 ± 0.6	3.7 ± 0.7	< 0.0001 **	0.139	< 0.0001 **	0.143
Body fluid removed (%body weight)	5.4 ± 1.5	4.0 ± 0.7	5.4 ± 0.4	7.3 ± 0.8	< 0.0001 **	0.139	< 0.0001 **	0.142
Ultrafiltration rate (ml/h)	744.7 ± 219.4	616.1 ± 192.3	729.3 ± 161.3	922.5 ± 184.4	< 0.0001 **	0.135	< 0.0001 **	0.151
Blood flow during dialysis (ml/min)	216.0 ± 20.5	212.9 ± 24.3	210.0 ± 10.5	225.5 ± 20.2	0.325			
Serum albumin concentration (g/dl)	3.7 ± 0.3	3.6 ± 0.3	3.7 ± 0.3	3.8 ± 0.2	0.138			
Serum sodium concentration (mEq/L)	138.6 ± 3.1	138.7 ± 2.1	139.0 ± 3.7	138.2 ± 3.9	0.893			
Serum chloride concentration (mEq/L)	103.9 ± 9.0	105.1 ± 3.6	106.3 ± 4.1	99.6 ± 15.2	0.380			
Serum potassium concentration (mEq/L)	4.9 ± 0.8	4.7 ± 1.0	5.0 ± 0.6	5.0 ± 0.5	0.559			
Serum calcium concentration (mEq/L)	8.7 ± 0.5	8.8 ± 0.5	8.6 ± 0.6	8.5 ± 0.6	0.936			
Serum phosphorus concentration (mEq/L	4.9 ± 0.8	4.7 ± 1.0	5.3 ± 1.1	5.0 ± 1.4	0.235			
Blood urea nitrogen (mg/dl)	59.3 ± 10.8	53.3 ± 10.5	64.4 ± 9.2	62.6 ± 9.3	0.029 *	0.060	0.105	1.000
Uric acid (mg/dl)	7.4 ± 1.8	7.2 ± 1.8	6.9 ± 0.9	8.2 ± 2.2	0.458			
Serum creatinine concentration (g/dl)	9.9 ± 2.4	9.4 ± 2.6	9.7 ± 1.9	10.6 ± 2.7	0.427			
LDL-cholesterol (mg/dl)	81.9 ± 27.8	83.2 ± 30.4	79.8 ± 26.3	83.6 ± 16.5	0.938			
Lactate dehydrogenase (IU/L)	168.5 ± 44.9	173.6 ± 56.4	163.2 ± 23.9	184.1 ± 29.1	0.067			
Creatine kinase (IU/L)	80.5 ± 36.7	89.4 ± 38.5	60.9 ± 27.6	87.7 ± 37.9	0.303			
Cholinesterase (IU/L)	219.8 ± 41.0	217.2 ± 56.1	230.4 ± 27.3	217.7 ± 81.9	0.400			
Total protein (g/dl)	6.5 ± 0.4	6.7 ± 0.4	6.4 ± 0.3	6.3 ± 0.4	0.074			
Hemoglobin (g/dl)	10.8 ± 1.1	10.9 ± 1.1	10.9 ± 1.0	10.6 ± 1.1	0.643			
Hematocrit (%)	33.1 ± 3.2	33.5 ± 3.1	33.9 ± 3.4	31.9 ± 3.2	0.460			
Human atrial natriuretic peptide (pg/ml)	74.2 ± 44.5	63.0 ± 34.6	80.1 ± 53.1	77.1 ± 45.6	0.829			
Protein catabolic rate (g/Kg/day)	0.86 ± 0.12	0.81 ± 0.12	0.89 ± 0.11	0.92 ± 0.12	0.050			
Kt/V	1.53 ± 0.29	1.40 ± 0.23	1.51 ± 0.31	1.71 ± 0.27	0.128			

Results reported as mean ± standard deviation (SD). Differences among the three groups were assessed by the Kruskal−Wallis test; if $P<0.05$, between–group comparisons were performed with the Mann–Whitney *U*–test. Abbreviations: LDL–C, low–density lipoprotein cholesterol; K−W, Kruskal−Wallis test. ** $P < 0.01$, *$P < 0.05$.

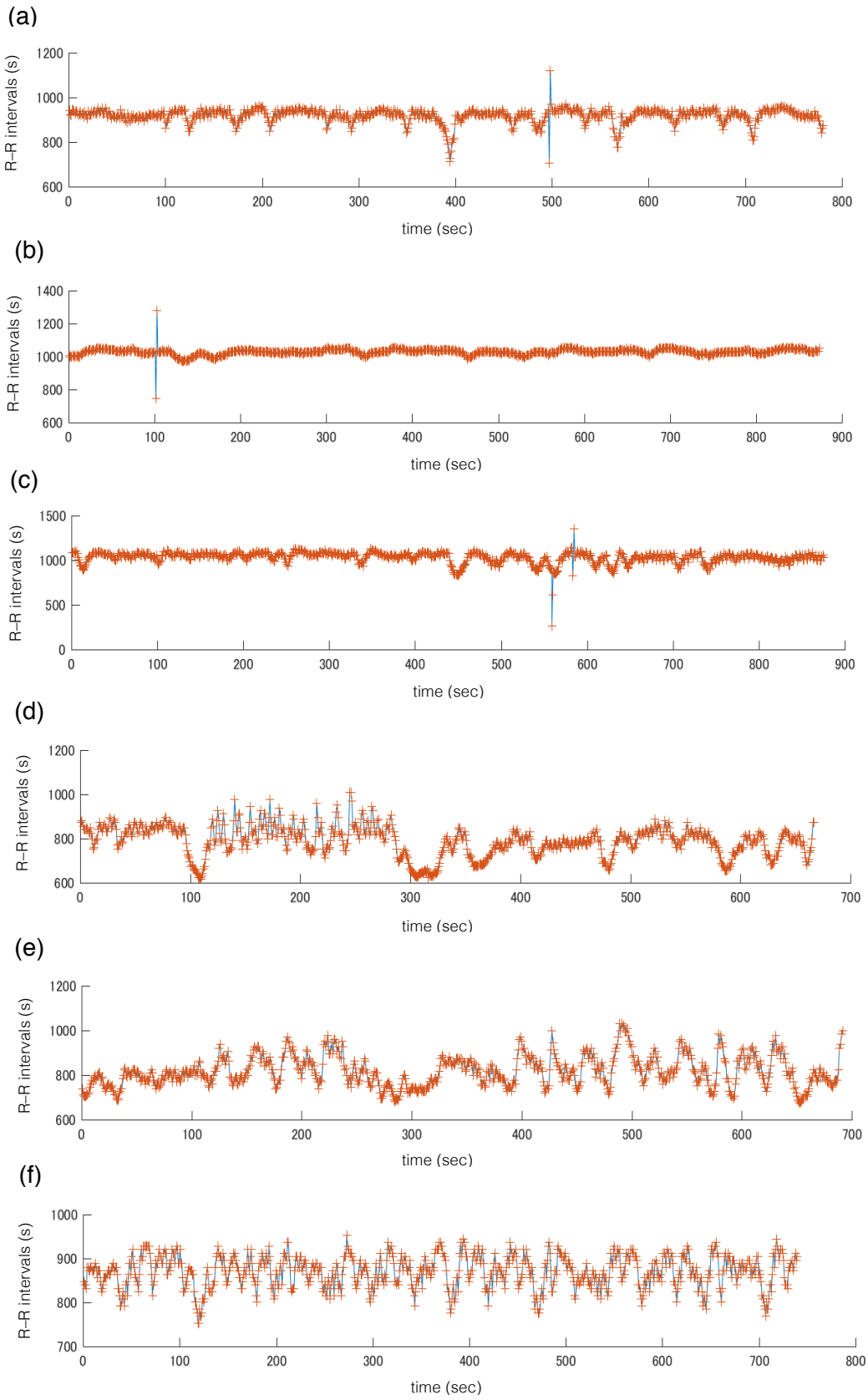


Figure 3.4 Examples of R−R intervals of ECG original data during hemodialysis session

R–R intervals for: (a)–(b), patients with UFR < 10 ml/hr/kg (Group I, n=14); (c)–(d), patients with 10 ml/hr/kg ≤ UFR ≤ 15 ml/hr/kg (Group II); and (e)–(f), patients with UFR >15 ml/hr/kg (Group III).

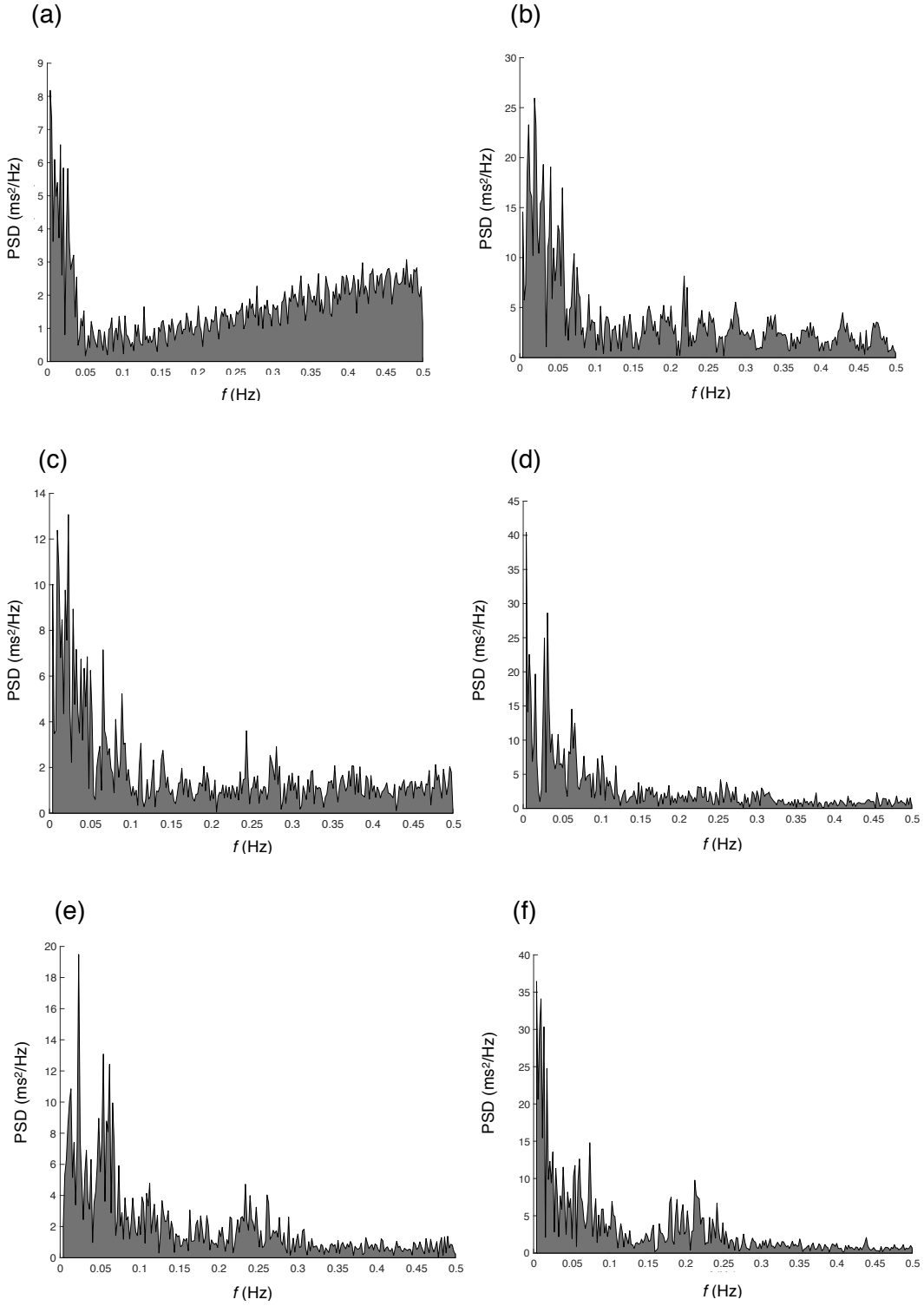
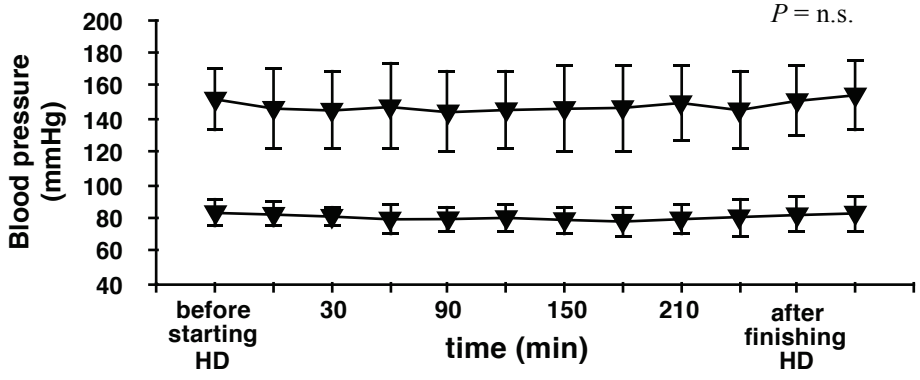
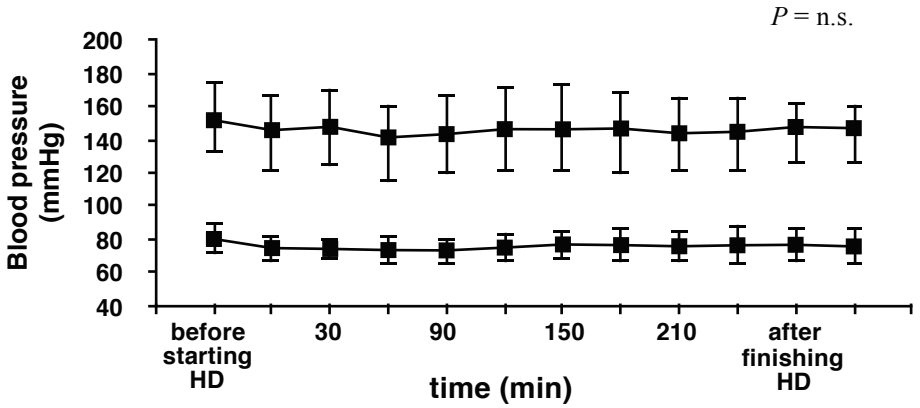


Figure 3.5 Examples of power spectrum density during hemodialysis session

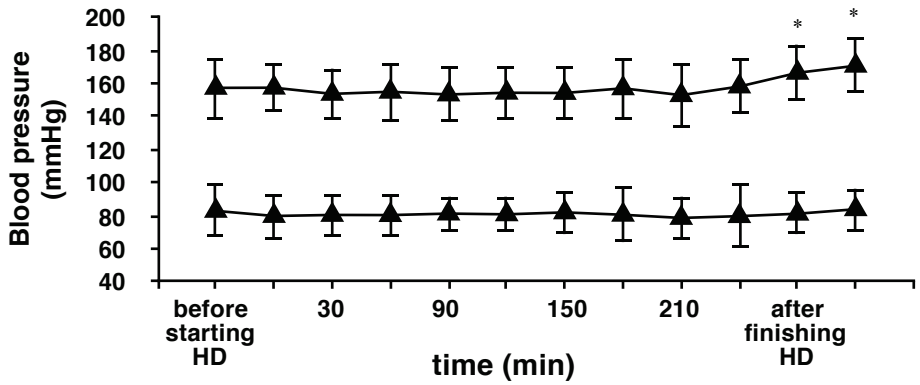
Power spectrum density for: (a)–(b) patients with UFR < 10 ml/hr/kg (Group I, n=14); (c)–(d), patients with 10 ml/hr/kg ≤ UFR ≤ 15 ml/hr/kg (Group II); and (e)–(f), patients with UFR >15 ml/hr/kg (Group III).



(a) UFR < 10 ml/hr/kg (Group I, n=14)



(b) 10 ml/hr/kg ≤ UFR ≤ 15 ml/hr/kg (Group II, n=10)

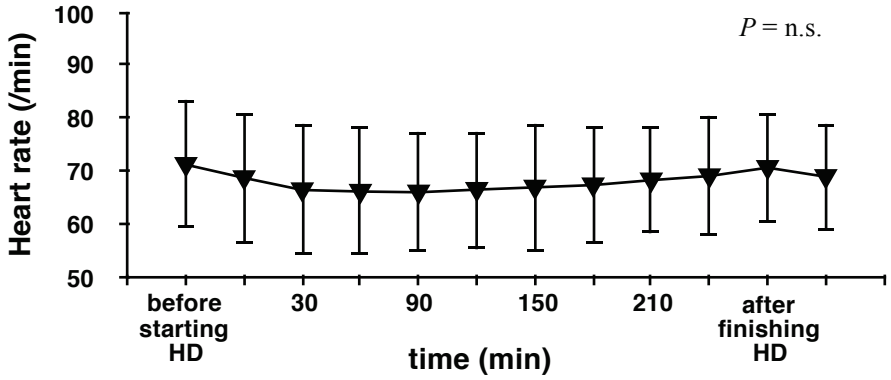


(c) UFR > 15 ml/hr/kg (Group III, n=11)

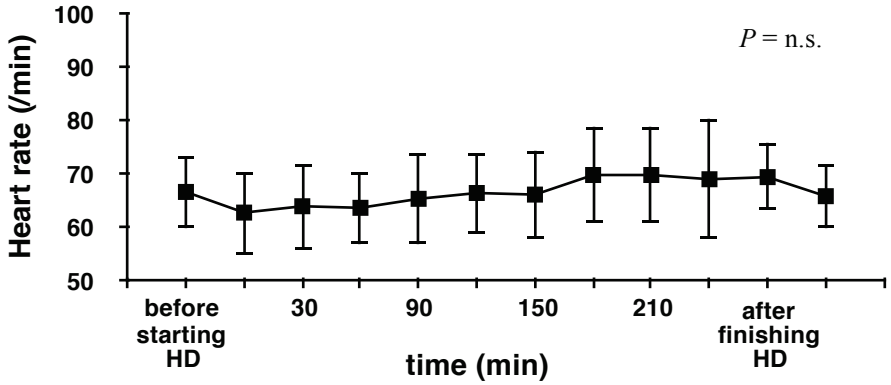
Figure 3.6 Blood pressure during HD in deference UFR.

Data are shown as mean ± standard deviation.

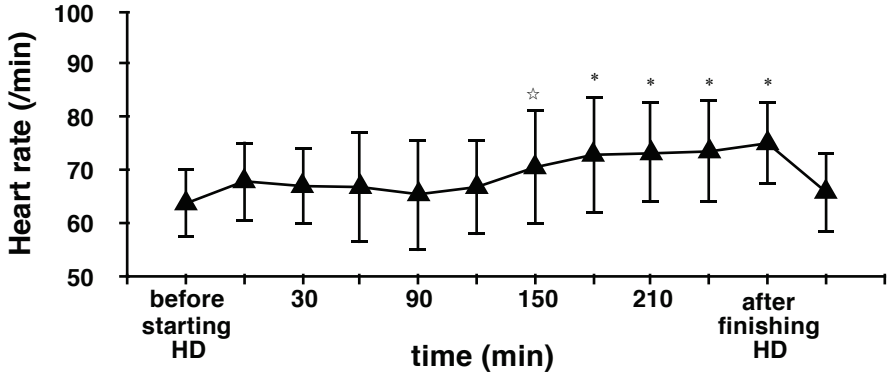
*$P < 0.05$ compared with the same group at base line (before HD).



(a) UFR < 10 ml/hr/kg (Group I, n=14)



(b) 10 ml/hr/kg ≤ UFR ≤ 15 ml/hr/kg (Group II, n=10)

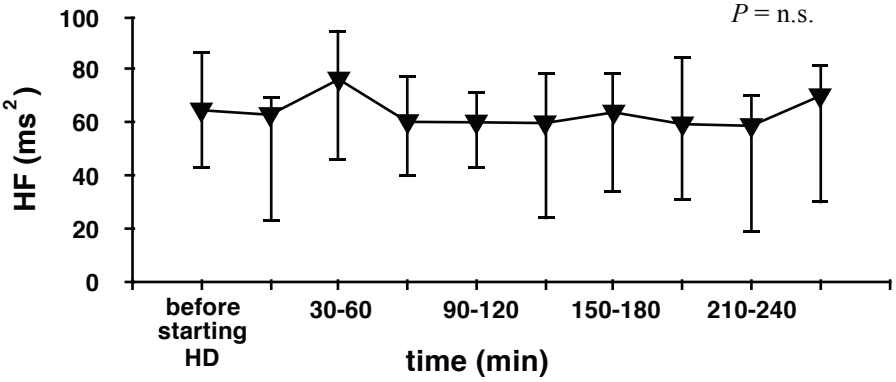


(c) UFR > 15 ml/hr/kg (Group III, n=11)

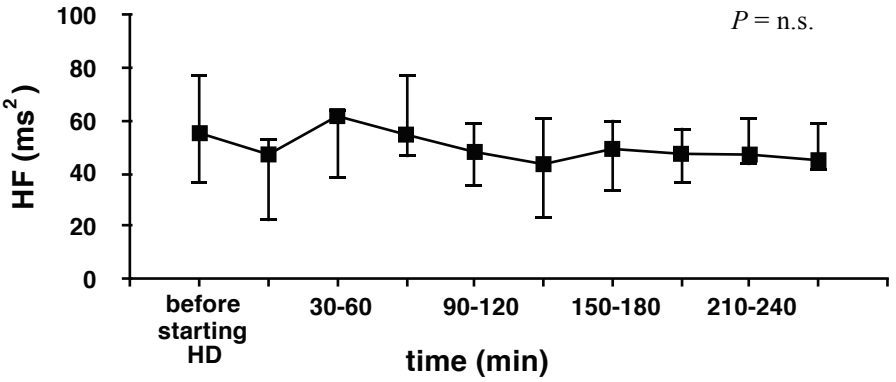
Figure 3.7 Heart rate during HD in deference UFR.

Data are shown as mean ± standard deviation.

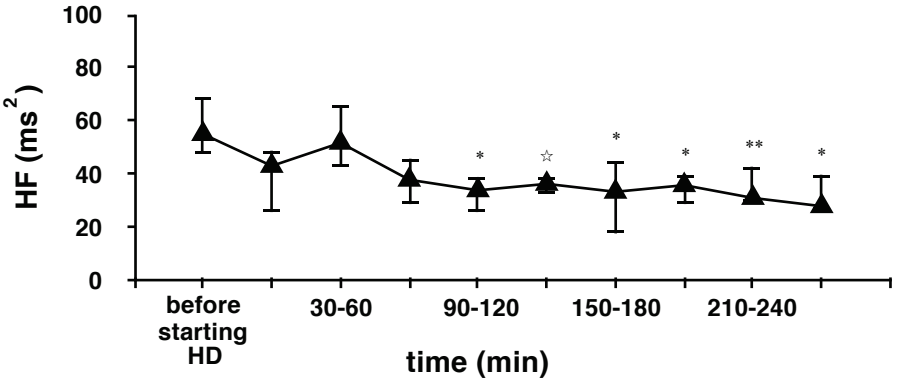
$^{**}P < 0.01$, $^{*}P < 0.05$, ☆$P < 0.1$ compared with the same group at base line (before HD).



(a) UFR < 10 ml/hr/kg (Group I, n=14)



(b) 10 ml/hr/kg ≤ UFR ≤ 15 ml/hr/kg (Group II, n=10)

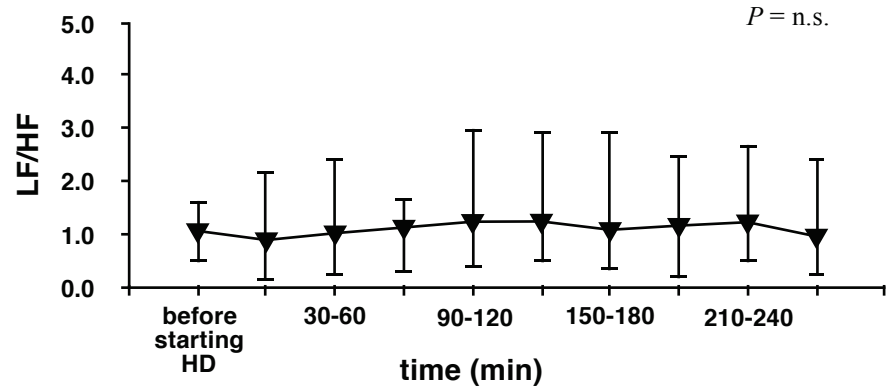


(c) UFR > 15 ml/hr/kg (Group III, n=11)

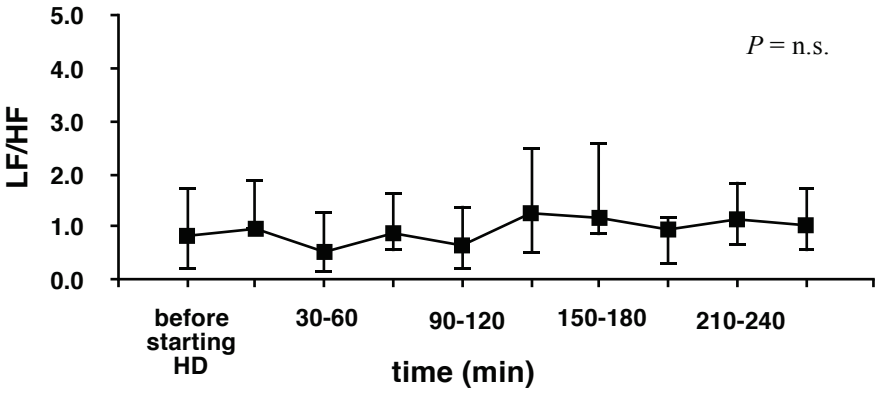
Figure 3.8 HF during HD in deference UFR.

Data are shown as medians changes with 25−75% interquartile range.

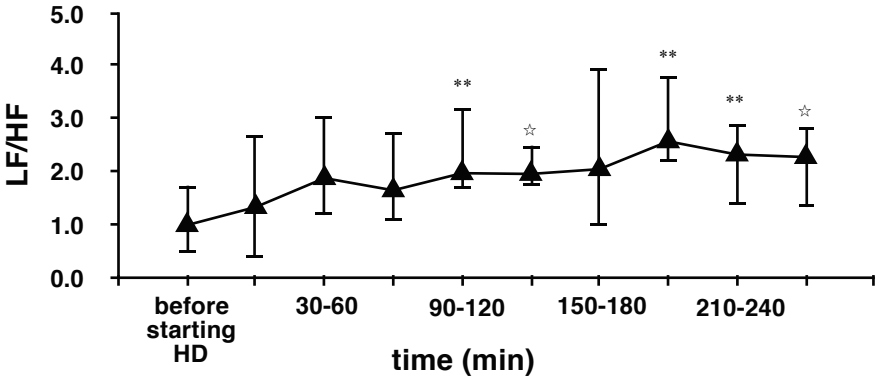
$^{**}P < 0.01$, $^{*}P < 0.05$, ☆$P < 0.1$ compared with the same group at base line (before HD).



(a) UFR < 10 ml/hr/kg (Group I, n=14)



(b) 10 ml/hr/kg ≤ UFR ≤ 15 ml/hr/kg (Group II, n=10)

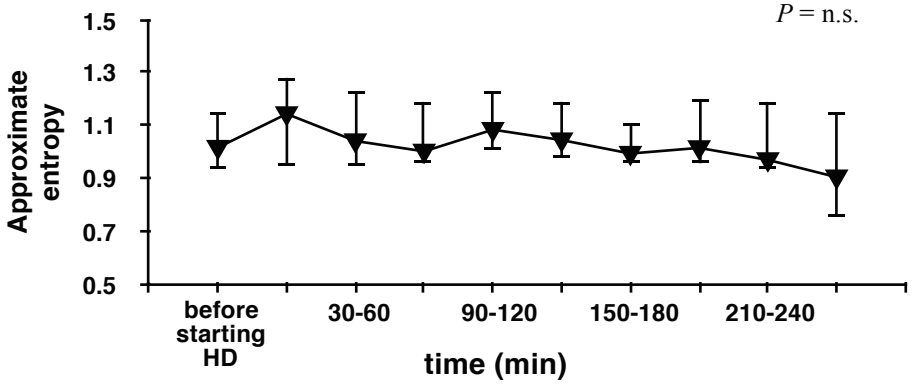


(c) UFR > 15 ml/hr/kg (Group III, n=11)

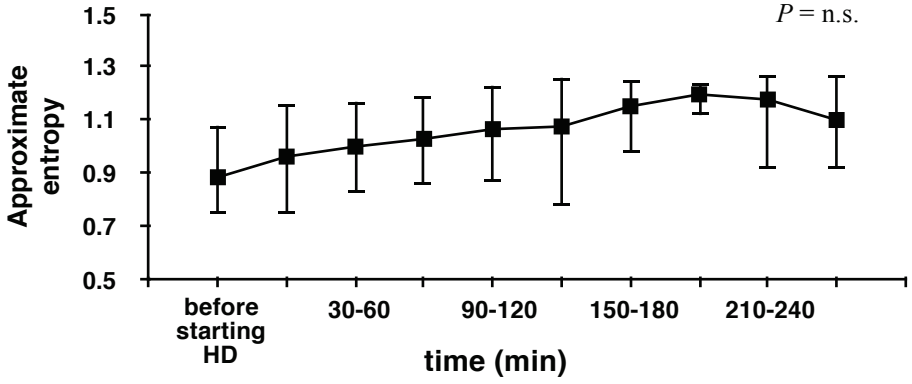
Figure 3.9 HF/LF during HD in deference UFR.

Data are shown as medians changes with 25−75% interquartile range.

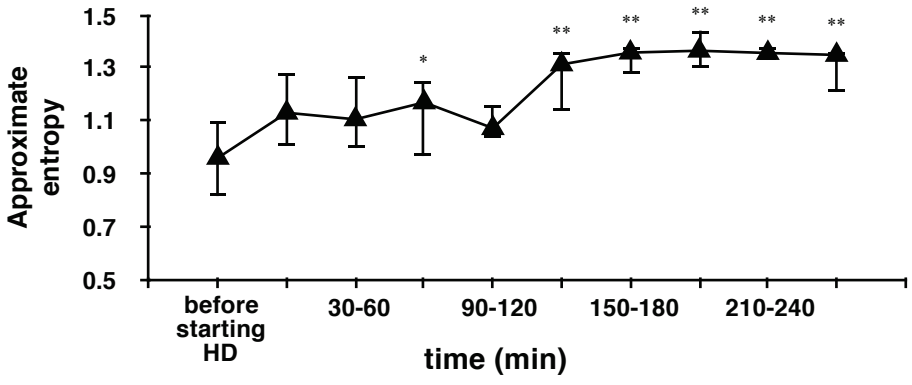
$^{**}P < 0.01$, $^{*}P < 0.05$, ☆$P < 0.1$ compared with the same group at base line (before HD).



(a) UFR < 10 ml/hr/kg (Group I, n=14)



(b) 10 ml/hr/kg ≤ UFR ≤ 15 ml/hr/kg (Group II, n=10)



(c) UFR > 15 ml/hr/kg (Group III, n=11)

Figure 3.10 Approximate entropy during HD in deference UFR.

Data are shown as medians changes with 25−75% interquartile range.
$^{**}P < 0.01$, $^{*}P < 0.05$ compared with the same group at base line (before HD).

3.4 Discussion

This study used HRV and ApEn analysis to assess functional changes in the autonomic nervous system during an HD session. Analysis of time and frequency domain measures of heart rate variability (HRV) from Holter ECG recordings is an accepted and noninvasive method of assessing autonomic nervous system activity. As instantaneous heart rate depends on the interaction between sympathetic and parasympathetic nervous activity, HRV analysis may lead to quantification of autonomic regulation of heart rate. Frequency domain analysis is a fractional determination method that differentiates activity of the sympathetic and parasympathetic nerves from R−R interval dynamics [15, 60]. HRV analysis is widely utilized as an index of cardiac autonomic dysfunction and modulation. ApEn is associated with increased or decreased activity of autonomic nervous system. Nonlinear methods of heart rate analysis provide information about the dynamics of heart rate, and are widely used to determine the status of the autonomic nervous system [64]. In addition to conventional frequency analysis, heart rate variability may be analyzed using nonlinear dynamics. In determining the fractal dimension from heart rate variability, it is possible to assess the complexity of the time series. The complexity of heart rate variability has been associated with the homeostasis of the circulatory system [66–67]. The unstable fluctuations system is apparently complicated. The more a system can be changed quickly, the greater its flexibility with respect to disturbances.

In patients with UFR >15 ml/hr/kg (Group III), systolic blood pressure was significantly higher. In group III, 15 ml/hr/kg < UFR, systolic blood pressure values of 15 minutes after finishing HD than before starting HD, and heart rate was significantly higher after finishing HD than before HD. Blood pressure and heart rate are controlled by an endogenous regulatory system, which responds to changes in the amount of blood flowing to the heart, and to contractile force due to the activity of the autonomic nervous system. An increase in heart rate without a variation in blood pressure is thought to be an aftereffect of a reduction in circulating plasma volume due to a delay in plasma refilling rate. These results indicated that the baroreceptor reflex compensates for the reduction in capacity. The increase in blood pressure after HD sessions may have been due to the interactive effects between an increase in circulating plasma volume and its reinfusion into the body and sympathicotonia. Blood pressure elevation, coupled with a reduction in heart rate, after HD may have been due to the negative feedback of the baroreceptor reflex on the increase in

circulating plasma volume due to reinfusion. Increased heart rate has been reported to correlate with myocardial ischemia is clearly related [68]. Increased heart rate five minutes before myocardial ischemia has been observed is in 89% of these patients [69], with the duration and/or degree of increased heart rate increasing along with the increased rate of ST depression [70]. Increased heart rate during the latter part of HD sessions suggests the possibility of transient myocardial ischemia due removal of excess water.

Compared with pre−HD levels, patients in groups I and II, with UFR ≤ 15 ml/hr/kg, showed no significant changes in LF/HF ratio and HF during and after HD sessions. In contrast, as water removal from patients with UFR >15 ml/hr/kg (Group III) increased, HF decreased and LF/HF decreased. In general, LF/HF and HF are indices of sympathetic and parasympathetic nervous activity, respectively. My findings showed that, about two hours after the start of HD, sympathetic activity showed a sustained increase, while parasympathetic activity showed a sustained decrease until the completion of the HD session. A report on the relationship between HRV and myocardial ischemia showed that LF/HF started to increase 30 minutes prior to a 73% ischemic attack (ST segment depression), followed about 20 minutes later by a decrease in HF [71]. Thus, changes in autonomic nervous activity and heart rate precede the appearance of myocardial ischemia. Temporary sympathetic overactivity stabilizes hemodynamics during HD. If the compensatory mechanism is not sufficient, sympathetic overactivity may be sustained. Thus, in patients with sustained elevated blood pressure despite the removal of a large amount of water, sympathetic activity may have overcompensated for blood pressure reduction due to water removal. Moreover, in patients with sustained blood pressure during HD and UFR >15 ml/hr/kg, sympathetic overactivity may also compensate for myocardial ischemia resulting from a delay in plasma refilling due to excessive water removal. A reduction of parasympathetic nervous function would remove restraints against arrhythmia induced by sympathetic nerves. The likelihood of lethal arrhythmia is would therefore be higher following arrhythmia suppression by parasympathetic nerves, as when cardiac autonomic nervous control function has been impaired.

My results showed that, in patients with UFR >15 ml/hr/kg, ApEn increased with increasing removal of water. Increased ApEn represents the complexity of heart rate variability [72]. This increase in complexity during the latter half HD in Group III represents an increase in the capacity of the circulatory system to adjust in attempting to maintain homeostasis. The effects of sympathetic and parasympathetic nervous

responses on regulating blood pressure in response to water removal may be expressed as an increase in the complexity of heart rate variability.

In conclusion, we show that high UFR are associated with an increase in sympathetic nervous overactivity in patients without blood pressure variation. This association deserves further studies using hemodynamic monitoring in order to prevent the mortality risk in patients on HD treatment. These findings help to decide the ultrafiltration volume for patients with higher body weight gains.

3.5 Limitations of this study

HRV may be influenced by multiple factors, including body motion, respiration, subject age, and cardiovascular medications. To estimate HRV, I could not fully remove selection or measurement bias. The backgrounds of HD patients differ, and the amounts of water removed vary daily. Thus, reproducibility could not be confirmed due to within subject differences in the amount of water removed. Moreover, I did not reach the estimated danger zone for overactivity of the sympathetic nervous system and did not determine the most suitable UFR for each patient based on changes in autonomic nervous activity. HRV measures are rather complex, and the physiological determinations are not well defined. Therefore, further research is needed to determine the effects of autonomic nervous activity during HD.

3.6 Conclusion

Sympathetic nervous stimulation elevates heart rate and enhances the contractile force of the myocardium. However, sympathetic nerve overactivity can cause sudden cardiac death or induce arrhythmia. Removing water at high UFR (>15 ml/hr/kg) enhances sustained sympathetic nervous overactivity. This study showed that high UFR was associated with an increase in sympathetic nervous overactivity and suggests that HD be performed at a UFR <15 ml/hr/kg.

Acknowledgment: The author thanks the staff of the dialysis center at Yodogawa Christian Hospital for their help with data collection.

Conflict of interest: The author declares no competing financial interests.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Yodogawa Christian Hospital and with the ethical standards of the institutional, and national research committee at which the studies were conducted (IRB approval number NCT02754986) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Chapter IV

Improvement of QOL Associated with Improving Constipation

4.1 Introduction

Hemodialysis patients often experience digestive symptoms including constipation [73−75]. These symptoms may be caused by fluid intake restriction, lack of dietary fiber due to potassium intake restrictions, lack of exercise, reduction of abdominal pressure, adverse drug reactions leading to hyperphosphatemia, and others. Appropriate bowel habits are necessary to prevent a perforation, ileus, and ischemia−related enteritis. In addition, the prevention and control of constipation are important because chronic constipation may substantially impact the QOL of hemodialysis patients. Generally, the bowel movement is a basic activity of daily living with important psychological and social significance for humans, as well as a biological need. Hemodialysis patients experience physical and social stresses due to their condition and treatment that make them susceptible to psychiatric symptoms. Hemodialysis is a treatment that patients must continue throughout their lives, and that puts patients in a situation that leads to uneasiness and stress. This stress on the mind and body causes dysautonomia, which is a strong risk factor for constipation [76].

In recent years, many studies have reported that *Bifidobacterium* is useful for humans, and widely used as a probiotic. Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit to the host, including the gastrointestinal tract [77]. The intake of probiotics increases the proportion of useful bacteria such as *Lactic acid bacteria* and *Bifidobacteria* in the bowels, and decreases the proportion of harmful bacteria. The toxic products produced by harmful bacteria, such as indole and ammonia, decrease, and the enteral environment is improved by the short−chain fatty acids that *lactic acid bacteria* produce increase. These factors contribute to the prevention and improvement of constipation. In addition, probiotics are useful for the improvement of autoimmune disease, inflammatory bowel disease, and hypersensitive colon syndrome and the relaxation of the stress response [78–79].

Previous studies have reported that probiotic administration was effective for the control of toxic product−producing enterobacterial flora in hemodialysis patients [80–81]. The blood phosphorus level of progressive chronic kidney failure patients was significantly decreased by taking a *Bifidobacterium* preparation [82]. However, few studies have focused on the psychological changes of hemodialysis patients associated with the improvement of constipation symptoms. The aim of this study was

to investigate the effect of enteric capsules containing *Bifidobacteria* on changes to QOL in hemodialysis patients with constipation.

4.2 Methods

4.2.1 Subjects

Thirty−two hemodialysis patients were examined. The following exclusion criteria were established to restrict the stable case. Exclusion criteria were as follows: 1) The case that a patient hopes for the cancellation to this study; 2) failure to take the *Bifidobacteria*−containing enteric capsules according to study guidelines; 3) occurrence of digestive disease or demonstrating clinical signs of gastrointestinal disease; 4) concurrent administration of a medication to treat constipation or diarrhea; 5) incomplete questionnaire; 6) change in the administration of concurrent medications that can affect laboratory findings; 7) The case that the investigator instructed the continuation of this research. The study protocol was approved by the Ethics Committee of the Yodogawa Christian Hospital.

4.2.2 An intake method and trial materials

The total observation period was 16 weeks. The first 8 weeks were the control period, and the second 8 weeks were the *Bifidobacteria*−containing enteric capsule intake period (Figure 4.2). One capsule of the study drug was taken orally each day after breakfast. Healthy foods such as oatmeal or yogurt were permitted for breakfast. The subjects were advised to continue their usual diet throughout the study period. The enteric capsules (*Bifidus* HD®; Morishita Jintan Co., Ltd). contained 2×10^9 colony forming units of *Bifidobacterium longum* JBL01 and 0.11 g of oligosaccharide (raffinose and lactulose). Previous studies have shown that *Bifidobacterium* in most medical products and health foods cannot survive because of its exposure to gastric juices before it reaches the intestine, thus imparting only a limited effect on the intestinal microflora. *Bifidobacterium longum* in powder form could not survive at all in a solution of pH 1.2. However, the use of a gastroresistant seamless capsule allows *Bifidobacterium longum* to survive even in a solution of pH 1.2. [83] and prevents

Bifidobacteria from being inactivated before reaching the intestines [84]. Figure 4.1 shows the structure of *Bifidobacterium longum* in a gastroresistant seamless capsule.

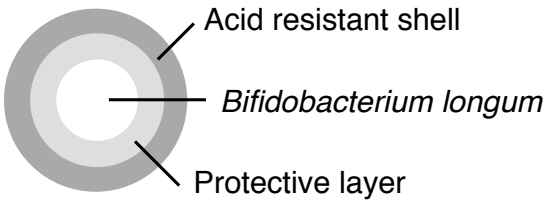


Figure 4.1 Structure of Enteric Capsule Preparation of *Bifidobacteria* formulation.

4.2.3 Constipation assessment scale (CAS)

The constipation assessment scale (CAS) developed and validated by McMillan and Williams (Table 4.1) has been adopted as an appropriate scale for assessing the presence of constipation [85]. The Japanese version of the CAS used in the present study (Table 4.2) has been verified as a subjective CAS [86]. This 8−item self−reported questionnaire designed to assess the presence and severity of constipation employs a 3−point summated rating scale (0: no problem, 1: some problem, 2: severe problem). The total score can range from 0 (no constipation) to 16 (severe constipation). A score of five points or more is considered to indicate constipation [87].

Subjects were asked to record their bowel frequency and rate the degree of constipation−associated symptoms using the CAS before beginning intake of the *Bifidobacteria*−containing enteric capsules and then at the beginning of each week during the observation period. Patients with a CAS score less than five points immediately before the intake period were excluded from analysis. The remaining subjects were divided into 3 groups according to the degree of improvement in constipation as reflected in CAS score: 1−4 week effective cases (CAS score was less than 5 points in the first 1−4 weeks); 5−8 week effective cases (CAS score was less

than 5 points in weeks 5−8); ineffective cases (CAS score did not fall below 5 points throughout the observation period).

The Bristol stool chart, which classifies feces into seven groups, was distributed to the subjects and used to assess the state of their stools. The scale is scored as follows: 1, separate hard lumps like nuts; 2, sausage−shaped but lumpy; 3, like a sausage or snake but with cracks on its surface; 4, like a sausage or snake, smooth and soft; 5, soft blobs with clear−cut edges; 6, fluffy pieces with ragged edges, a mushy stool; and 7, watery, no solid pieces [88].

Table 4.1 Constipation Assessment Scale [85]

Problem	No	Some	Severe
1. Abdominal distention	0	1	2
2. Change in amount of gas passed rectally	0	1	2
3. Reduced frequency of evacuations	0	1	2
4. Sensation of rectal pressure or fullness	0	1	2
5. Pain in rectal and/or anal region during evacuation	0	1	2
6. Reduced fecal caliber	0	1	2
7. Difficulty eliminating feces	0	1	2
8. Oozing liquid stool	0	1	2

Table 4.2 Japanese Version of Constipation Assessment Scale [86]

質問項目	No	Some	Severe
1. お腹の張った感じ	0	1	2
2. 排ガスの量	0	1	2
3. 排便の回数	0	1	2
4. 直腸に内容が充満している感じ	0	1	2
5. 排便時の肛門の痛み	0	1	2
6. 便の量	0	1	2
7. 便の排泄状態	0	1	2
8. 下痢様または水様便	0	1	2

CAS is an 8 items self report measure designed to assess the presence and severity of constipation. It consists of 3 point summated rating scale (0: no problem, 1: some problem, 2: severe problem). A total score is calculated that can range from 0 (no constipation) to 16 (severe constipation).

4.2.4 PAC−QOL

The Patient Assessment of Constipation Quality of Life Questionnaire (PAC−QOL), a validated questionnaire for the assessment of QOL in patients with chronic constipation, consists of four sub−scales to reflect physical discomfort, psychosocial distress, concerns, and satisfaction, with a total of 28 items (Table 4.3). Table 4.4 shows the PAC−QOL in Japanese. Patients evaluated each item on the PAC−QOL on a 5−pointscale ranging from 0, not at all or none of the time, to 4, extremely or all of the time. A lower score indicates a better QOL [89]. Subjects were asked to record their PAC−QOL score before and 6 weeks after intake of *Bifidobacteria*−containing enteric capsules. Questions 25−28 related to "Satisfaction" were treated as reversal items, with scores reverse−coded. Thus, each of these items was also considered in terms of "Dissatisfaction."

4.2.5 Blood tests

The blood tests were performed immediately before the intake period; and 4, 6, and 8 weeks after the start of the intake period (Figure 4.2). The following concentrations were measured: serum phosphorus (P), blood urea nitrogen (BUN), serum sodium (Na), serum chloride (Cl), serum potassium (K), serum creatinine (Cre), hemoglobin (Hb), serum calcium (Ca), and serum albumin (Alb). All parameters were measured before the start of a hemodialysis session. Blood tests were scheduled according to the schedule of the treatment facility. Calcium was normalized to serum albumin concentration.

4.2.6 Collection of patient information

Sex, age, height, dry weight (DW), body mass index (BMI), hemodialysis duration, hemodialysis time, and blood flow during hemodialysis were examined immediately prior to the start of intake (Figure 4.2).

Table 4.3 Patient Assessment of Constipation Quality of Life Questionnaire [89]

Domein/Item	Score
Physical discomfort	
1. have you felt bloated to the point of bursting?	0 – 1 – 2 – 3 – 4
2. have you felt heavy because of your constipation?	0 – 1 – 2 – 3 – 4
3. have you felt any physical discomfort?	0 – 1 – 2 – 3 – 4
4. have you felt the need to open your bowel but not been able to?	0 – 1 – 2 – 3 – 4
5. have you been embarrassed to be with other people?	0 – 1 – 2 – 3 – 4
Psychosocial discomfort	
6. have you been eating less and less because of not being able to have bowel movements?	0 – 1 – 2 – 3 – 4
7. have you had to be careful about what you eat?	0 – 1 – 2 – 3 – 4
8. have you had a decreased appetite?	0 – 1 – 2 – 3 – 4
9. have you been worried about not being able to choose what you eat (for example, at friend's)?	0 – 1 – 2 – 3 – 4
10. have you been embarrassed about staying in the toilet for so long when you were away from home?	0 – 1 – 2 – 3 – 4
11. have you been embarrassed about having to go to the toilet so often when you were away from home?	0 – 1 – 2 – 3 – 4
12. have you felt irritable because of your condition?	0 – 1 – 2 – 3 – 4
Worries/concerns	
13. have you been upset by your condition?	0 – 1 – 2 – 3 – 4
14. have you felt obsessed by your condition?	0 – 1 – 2 – 3 – 4
15. have you felt stressed by your condition?	0 – 1 – 2 – 3 – 4
16. have you been less self-confident because of your condition?	0 – 1 – 2 – 3 – 4
17. have you felt in control of your situation?	0 – 1 – 2 – 3 – 4
18. have you been worried about having to change your daily routine (for example, travelling, being away from home)?	0 – 1 – 2 – 3 – 4
19. have you been worried about not knowing when you are going to be able to open your bowels?	0 – 1 – 2 – 3 – 4
20. have you been worried about not being able to open your bowels when you needed to?	0 – 1 – 2 – 3 – 4
21. have you been more and more bothered by not being able to open your bowels?	0 – 1 – 2 – 3 – 4
22. have you been afraid that your condition will get worse?	0 – 1 – 2 – 3 – 4
23. have you felt that your body was not working properly?	0 – 1 – 2 – 3 – 4
Satisfaction	
24. have you had fewer bowel movements than you would like?	0 – 1 – 2 – 3 – 4
25. have you been satisfied with how often you open your bowels?	0 – 1 – 2 – 3 – 4
26. have you been satisfied with the regularity with which you open your bowels?	0 – 1 – 2 – 3 – 4
27. have you been satisfied with your bowel function?	0 – 1 – 2 – 3 – 4
28. have you been satisfied with your treatment?	0 – 1 – 2 – 3 – 4

Table 4.4 Patient Assessment of Constipation Quality of Life Questionnaire in Japanese

Domein/Item	Score
Physical discomfort	
1. 腹部がはちきれそうなくらい張っていると感じましたか？	0 – 1 – 2 – 3 – 4
2. 便秘のせいで体が重くなったように感じましたか？	0 – 1 – 2 – 3 – 4
3. 体に不快を感じましたか？	0 – 1 – 2 – 3 – 4
4. 排便しなければと思ったのに, 出ないことがありましたか？	0 – 1 – 2 – 3 – 4
5. 他の人といっしょにいて, 恥ずかしいと感じることがありましたか？	0 – 1 – 2 – 3 – 4
Psychosocial discomfort	
6. 他の人といっしょにいて, 恥ずかしいと感じることがありましたか？	0 – 1 – 2 – 3 – 4
7. 食べるものに気をつける必要がありましたか？	0 – 1 – 2 – 3 – 4
8. 食欲が落ちましたか？	0 – 1 – 2 – 3 – 4
9. （例えば友人宅などで）自分が食べる物を選ぶことができないと心配に感じたことはありましたか？	0 – 1 – 2 – 3 – 4
10. 外出中に, トイレに長時間入っていることで恥ずかしい思いをしたことはありますか？	0 – 1 – 2 – 3 – 4
11. 外出中に, トイレに何度も行くことで恥ずかしい思いをしたことはあります	0 – 1 – 2 – 3 – 4
12. 旅行中や外出中に, 生活のリズムが変わってしまうことで心配になることがありましたか？	0 – 1 – 2 – 3 – 4
Worries/concerns	
13. 便秘のせいでイライラすることがありましたか？	0 – 1 – 2 – 3 – 4
14. 便秘のせいで気持ちの動揺がありましたか？	0 – 1 – 2 – 3 – 4
15. 便秘のことで頭がいっぱいになることがありましたか？	0 – 1 – 2 – 3 – 4
16. 便秘によるストレスを感じることがありましたか？	0 – 1 – 2 – 3 – 4
17. 便秘のせいで自分に自信を持てなくなることがありましたか？	0 – 1 – 2 – 3 – 4
18. 自分がおかれている状況をコントロールできていると感じましたか？	0 – 1 – 2 – 3 – 4
19. いつ便意を催すかわからないので, 心配でしたか？	0 – 1 – 2 – 3 – 4
20. 排便する必要があるときにできないかもしれないと心配でしたか？	0 – 1 – 2 – 3 – 4
21. 排便できないことでますます心配になることがありましたか？	0 – 1 – 2 – 3 – 4
22. 症状が悪化するのではないかと不安になりましたか？	0 – 1 – 2 – 3 – 4
23. 体が正常に機能していないと感じましたか？	0 – 1 – 2 – 3 – 4
Satisfaction	
24. 自分が期待したより排便の回数が少ないと感じましたか？	0 – 1 – 2 – 3 – 4
25. 排便の回数について満足していますか？	0 – 1 – 2 – 3 – 4
26. 自分の排便の周期に満足していますか？	0 – 1 – 2 – 3 – 4
27. 腸の働きに満足していますか？	0 – 1 – 2 – 3 – 4
28. 受けた治療に満足していますか？	0 – 1 – 2 – 3 – 4

4.2.7 Statistical analysis

For the comparison of patient information, effective cases were defined as those showing an effect in 1−4 weeks (N=14) or 5−8 weeks (N=7). Data are shown as mean (standard deviation). *P* values are for the comparison between study groups. Fisher's exact probability test was used to compare sex and DM; the Mann−Whitney *U* test was used for patients' mean age, height, DW, BMI, duration of hemodialysis, hemodialysis time, and blood flow during hemodialysis. The Kruskal−Wallis test was used to compare CAS scores between periods, with data shown as median changes with interquartile range. If the Kruskal−Wallis test (comparison between two periods) yielded a *P* value of <0.05, between−period comparisons were performed with the Mann−Whitney *U* test. The Wilcoxon signed−rank test was used to compare PAC−QOL score before intake and at 6 weeks, with data shown as median changes with interquartile range. The Kruskal−Wallis test was used for comparisons between groups, and if it yielded a *P* value <0.05, between−group comparisons were performed with the Dunn test. The Wilcoxon signed−rank test was used to compare the results of blood tests before intake and during each period, with data shown as median changes with interquartile range.

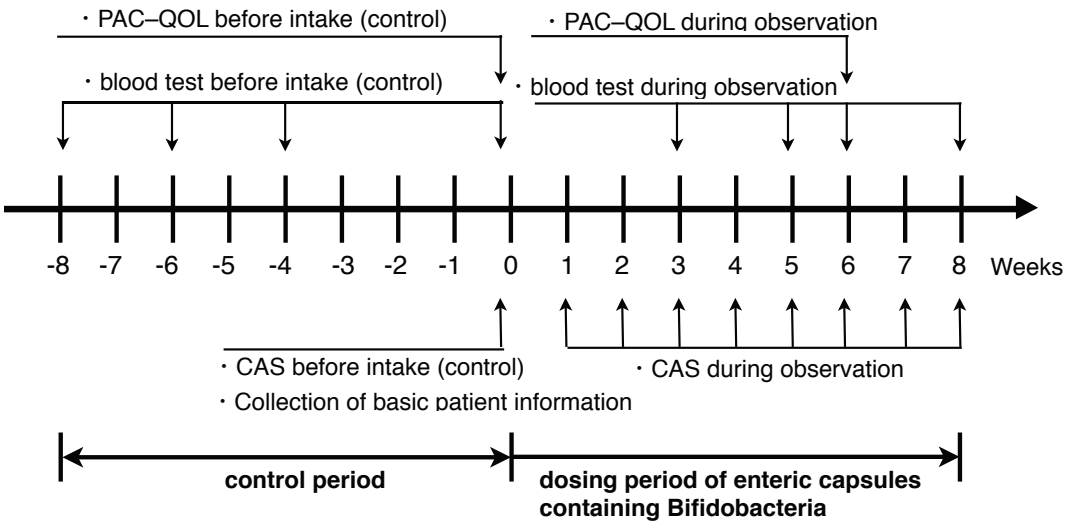


Figure 4.2 Schematic schedule for implementation time of each test

4.3 Results

4.3.1 CAS

1) Classification of subjects by CAS score

The results (*P* values) of the Fisher's exact tests and Mann−Whitney *U* tests performed to examine the differences in CAS scores between groups are summarized in Table 4.5. Thirty−two patients were recruited for the study. During the 8−week follow−up period, five patients withdrew from the study, three because they no longer wished to participate in the trial, one due to a change in phosphorus binder, and one due to undergoing large intestine endoscopy during the observation period. In total, 24 patients were enrolled as subjects. Twenty−one patients (90.6%) suffered from constipation, and three patients (9.4%) did not. Constipation was significantly improved in 21 patients (87.5%) and was not improved in 3 patients (12.5%)

2) Comparison of subjects based on effectiveness

Table 4.5 shows subject characteristics. The mean age of effective cases was significantly higher than that of ineffective cases (*P*=0.0128). DW, height, and the number of DM were significantly lower in effective cases than in ineffective cases (*P*=0.0232, *P*=0.0088, and *P*=0.0441, respectively). The BMI in effective cases tended to be lower than that in ineffective cases (*P*=0.0807). No other items significantly differed between effective and ineffective cases.

3) Changes in the CAS total score

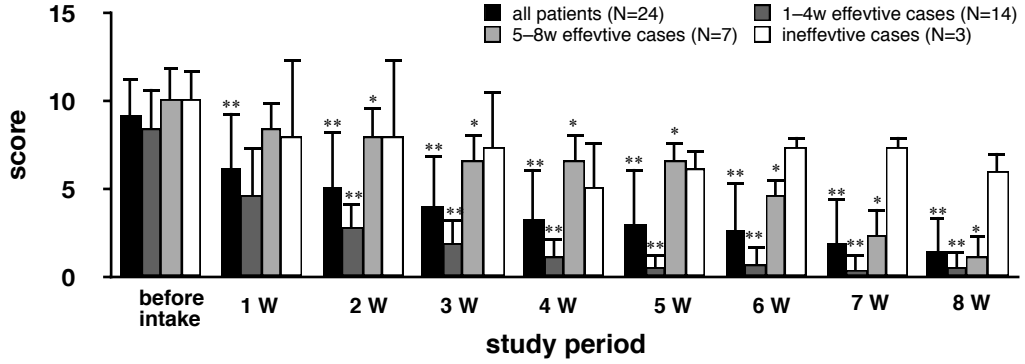
Figure 4.3 shows the changes in CAS score, with asterisks indicating a significant difference between before intake and each period. Subjects' mean total score before intake of *Bifidobacteria*−containing enteric capsules was 9.1 points. The score before starting intake of *Bifidobacteria*−containing enteric capsules was 6.2 points, after 2 weeks was 5.0 points, after 3 weeks was 4.0 points, and remained less than 5 points for the rest of the observation period. The score at the end of the observation period was significantly lower than the score before intake (*P*=0.0071). In 1–4 week effective cases, the score before intake was 8.4 points, after 1 week was 4.6 points,

and after 2 weeks was 2.8 points, with the score after 2 weeks significantly lower than that before intake ($P \leq 0.0001$). In 5–8 week effective cases, the score before intake was 10.1 points, after 6 week was 4.6 points, and after 2 weeks was 2.8 points. The score after 3 weeks later was significantly lower than the score before intake ($P=0.0409$). In ineffective cases, the CAS score before intake was 10.0 points, and that after 8 weeks was 6.0 points, with no significant differences between measurements over the observation period.

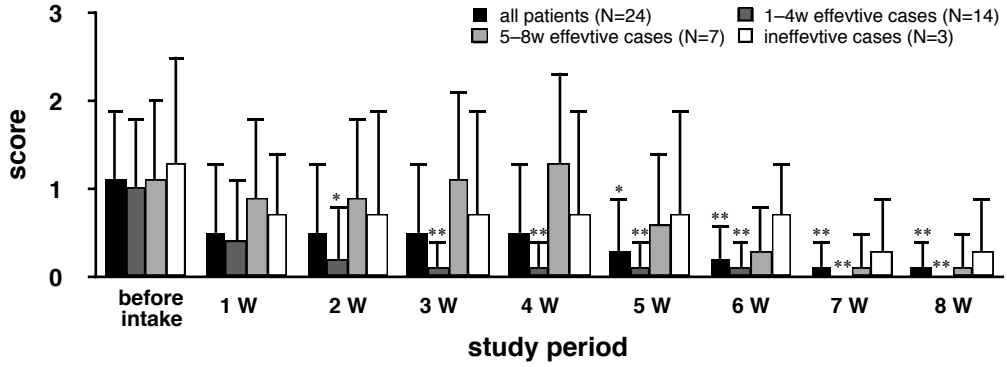
Table 4.5 Baseline characteristics per study group by improving result of constipation

	All Patients (N = 24)		***P*–value**	
	effective cases (N = 21)	ineffective cases (N = 3)		
Males / females	9 / 12	3 / 0	0.0641	☆
Mean age, yr (SD)	64.6 (7.7)	48.0 (10.6)	0.0128	*
Height, cm (SD)	158.5 (9.1)	168.5 (8.7)	0.0088	**
DW , kg (SD)	54.3 (11.1)	76.5 (12.8)	0.0232	*
BMI, kg/m^2 (SD)	21.5 (2.9)	27.1 (5.4)	0.0807	☆
Duration of HD, yr (SD)	5.2 (4.5)	1.4 (0.6)	0.1263	
HD time, hr (SD)	4.0 (0.2)	4.3 (0.6)	0.1286	
Blood flow during dialysis, ml/min (SD)	224.3 (20.6)	230.0 (36.1)	0.8894	
DM / non DM	8 / 13	3 / 0	0.0441	*

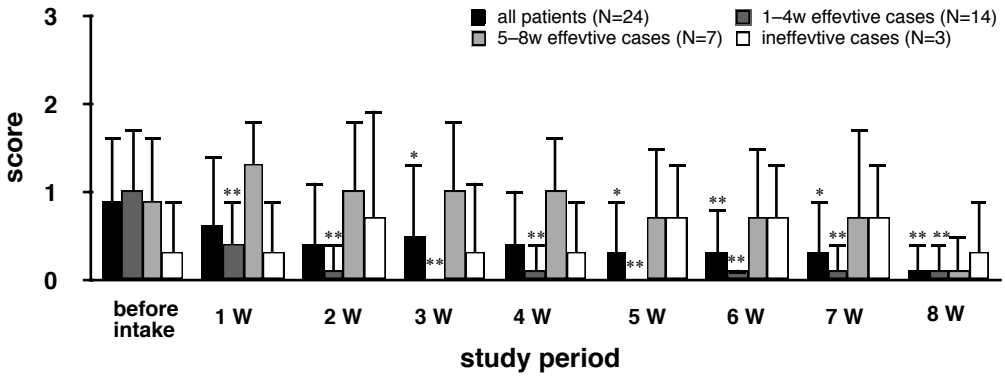
DW, dry weight; BMI, body mass index; HD, hemodialysis; DM, diabetes mellitus. Effective cases consists of 1–4w effective cases (N=14) and 5–8w effective cases (N=7). Data are shown as mean (standard deviation). *P*–values are for the comparison between study groups. Fisher's exact probability tests were used for gender and DM; Mann–Whitney *U*–test were used for mean age, height, DW, BMI, duration of HD, HD time and blood flow during dialysis of patients. The asterisk indicates the significant difference between before intake and 6w. The star indicates the tendency between before intake and 6w. ☆: $P<0.1$, *: $P<0.05$, **: $P<0.01$



(a) Total Score of CAS



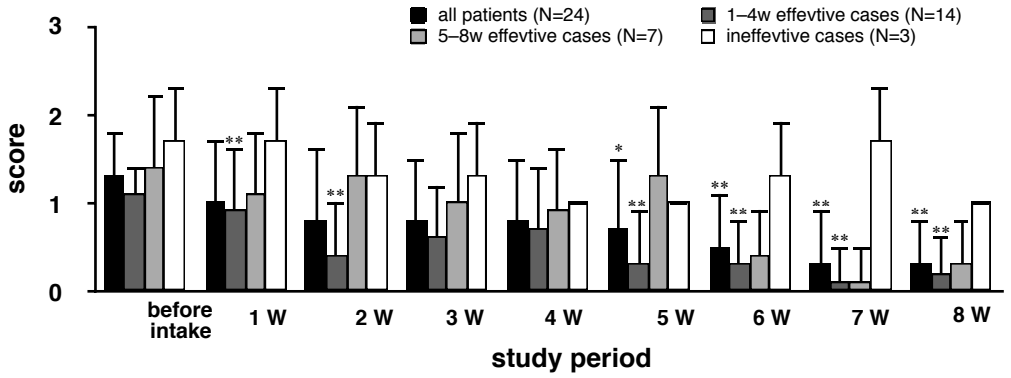
(b) Score of Abdominal distention



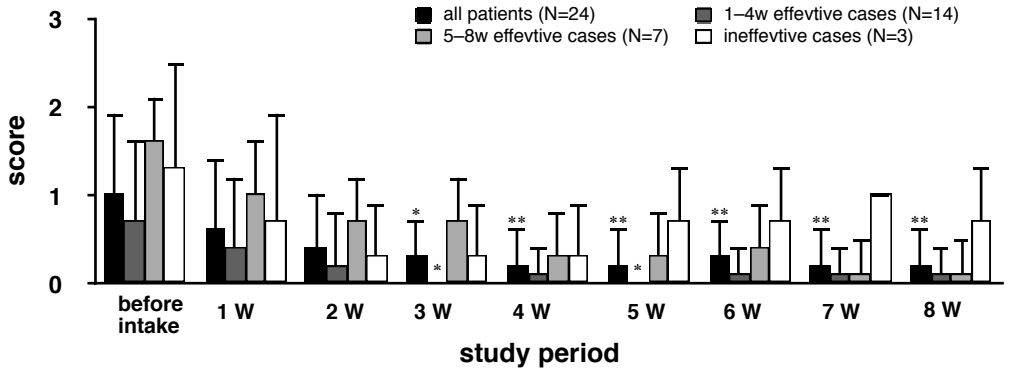
(c) Score of Change in amount of gas expelled

Figure 4.3 (a)−(c) Result of CAS during the observation period (8W)

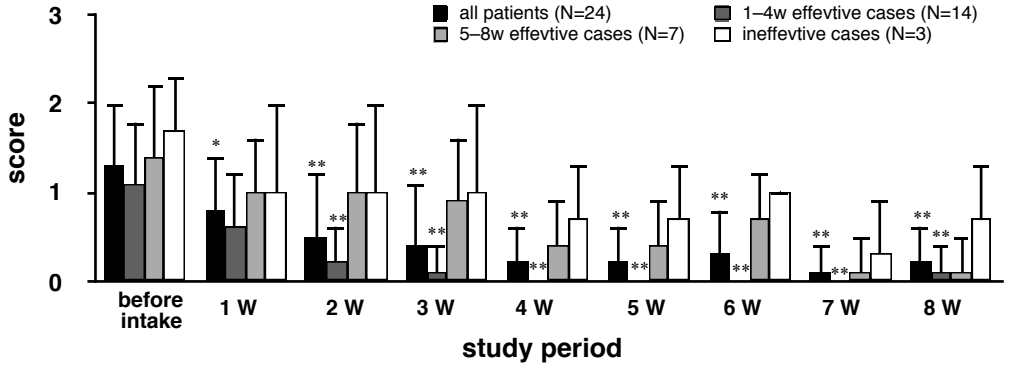
Data are shown as median changes with interquartile range. The asterisk indicates the significant difference between before intake and each period.
** $P < 0.01$, * $P < 0.05$.



(d) Score of reduced frequency of evacuations



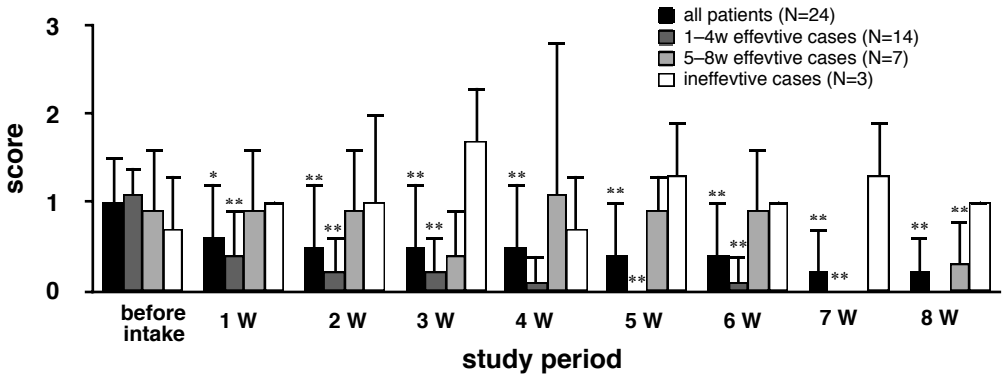
(e) Score of sensation of rectal pressure of fullness



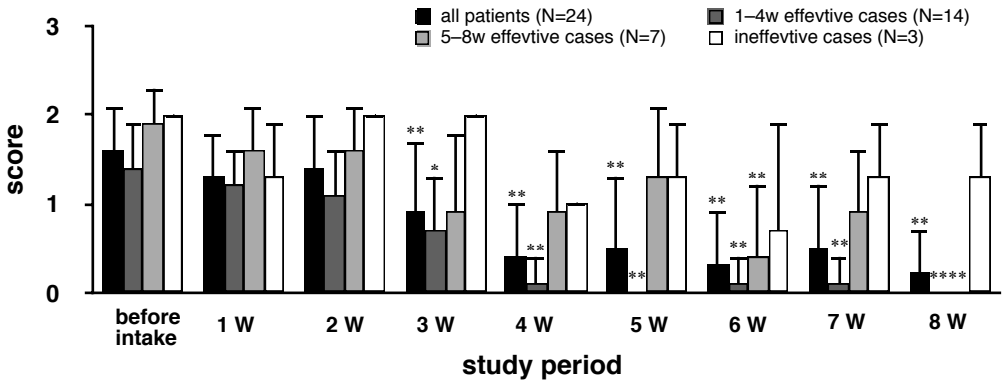
(f) Score of pain in rectal and/or anal region during evacuation

Figure 4.3 (d)−(f) Result of CAS during the observation period (8W)

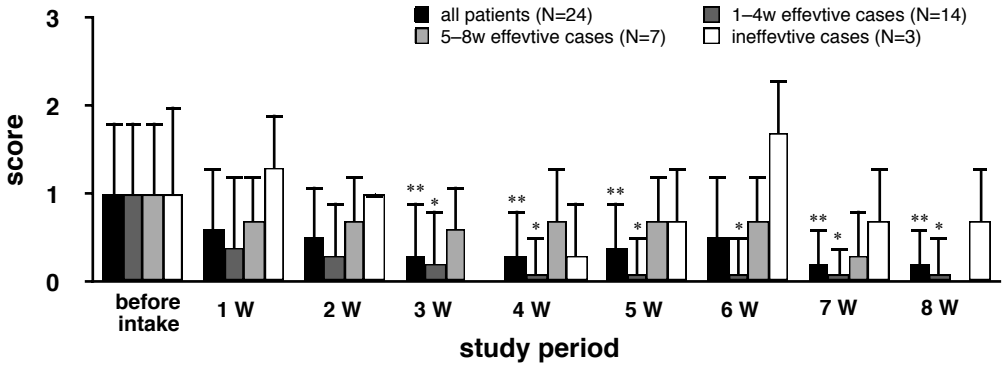
Data are shown as median changes with interquartile range. The asterisk indicates the significant difference between before intake and each period. ** $P < 0.01$, *$P < 0.05$.



(g) Score of reduced fecal caliber



(h) Score of difficulty eliminating feces



(i) Score of oozing liquid stool

Figure 4.3 (g)−(i) Result of CAS during the observation period (8W)

Data are shown as median changes with interquartile range. The asterisk indicates the significant difference between before intake and each period.
** $P < 0.01$, *$P < 0.05$.

4.3.2 PAC−QOL

(1) Comparison of PAC–QOL scores

Table 4.6 shows the changes in PAC−QOL score. The total score before intake of *Bifidobacteria*−containing enteric capsules was 41.5 points. The total score 6 weeks later was 13.5 points, reflecting a significant decrease from the pre−intake score (P<0.0001). The scores for physical discomfort, psychological discomfort, worries/ concerns, and dissatisfaction were significantly lower after 6 weeks than before intake (P<0.0001, P=0.0032, P=0.0027, and P<0.0001, respectively).

(2) Comparison between the group by PAC–QOL score

In 1–4 week effective cases, the physical discomfort, psychological discomfort, worries/concerns, and dissatisfaction scores were significantly lower after 6 weeks than before intake (P<0.0001, P=0.0107, P=0.0096, and P<0.0001, respectively). In 5–8 week effective cases, the physical discomfort, worries/concerns, and dissatisfaction scores were significantly lower after 6 weeks than before intake (P=0.0016, P=0.0239, and P=0.0025, respectively). In ineffective cases, the physical discomfort score was significantly lower after 6 weeks than before intake (P=0.0463).

4.3.3 Blood test results

Figures 4.4−4.6 show the results of blood tests during the observation period. In 1–4 week effective cases, serum phosphorus values were significantly lower after 3 weeks and 5 weeks compared to before intake (P=0.0255, P=0.0177). Blood urea nitrogen levels were significantly lower after 3 weeks than before intake (P=0.0408). There were no other significant differences in blood test findings during the observation period.

Table 4.6 Changes according to the question items of PAC−QOL in 6 weeks

		before intake	6W	*P*–value
Physical discomfort	All patients (N=24)	10.5 (13.5–7.8)	1.0 (3.3–0.0)	<.0001 **
(16–point scale)	1–4w effective cases (N=14)	10.5 (12.5–7.0)	0.0 (1.0–0.0)	<.0001 **
	5–8w effective cases (N=7)	10.0 (14.5–8.0)	2.0 (3.0–0.5)	0.0016 **
	ineffective cases (N=3)	16.0 (16.0–8.5)	10.0 (10.5–6.5)	0.5066
Psychological discomfort	All patients (N=24)	7.0 (12.3–3.8)	3.0 (4.3–2.0)	0.0032 **
(32–point scale)	1–4w effective cases (N=14)	5.0 (12.8–4.0)	2.5 (3.8–0.5)	0.0107 *
	5–8w effective cases (N=7)	7.0 (8.0–5.0)	4.0 (5.5–2.5)	0.0952 ☆
	ineffective cases (N=3)	12.0 (14.5–7.0)	3.0 (4.5–3.0)	0.5066
Worries / concerns	All patients (N=24)	11.5 (24.3–7.8)	3.0 (9.3–0.0)	0.0027 **
(44–point scale)	1–4w effective cases (N=14)	10.0 (24.8–4.8)	3.0 (8.3–0.0)	0.0096 **
	5–8w effective cases (N=7)	12.0 (14.5–9.5)	3.0 (9.0–0.5)	0.0239 *
	ineffective cases (N=3)	14.0 (21.0–7.0)	13.0 (19.5–8.5)	0.8273
Dissatisfaction	All patients (N=24)	13.5 (14.3–12.0)	3.0 (5.3–1.0)	<.0001 **
(20–point scale)	1–4w effective cases (N=14)	12.0 (14.0–12.0)	3.0 (5.8–1.0)	<.0001 **
	5–8w effective cases (N=7)	8.0 (11.5–5.5)	3.0 (3.5–1.0)	0.0025 **
	ineffective cases (N=3)	14.0 (14.0–13.5)	8.0 (9.0–4.0)	0.0463 *
total score	All patients (N=24)	41.5 (63.0–30.5)	13.5 (20.0–6.0)	<.0001 **
(112–point scale)	1–4w effective cases (N=14)	45.0 (64.3–34.0)	11.0 (16.0–6.0)	<.0001 **
	5–8w effective cases (N=7)	33.0 (49.0–32.0)	13.0 (17.5–8.0)	0.0017 **
	ineffective cases (N=3)	60.0 (65.0–38.5)	37.0 (39.5–27.5)	0.5127

PAC−QOL is a validated questionnaire which assesses 28 items grouped into four subscales: physical discomfort, psychosocial discomfort, worries/concerns, and dissatisfaction. An items are rated on a 5 point scale from 0 to 4, and scores are reported as an average total score or subscale score. Data are shown as median changes with interquartile range. Wilcoxon signed–rank test were used for the comparison between before intake and 6w. Kruskal–Wallis test were used for the comparison between each group. If the Kruskal–Wallis test (comparison between each group) yield a value of $P<0.05$, between each group comparisons were performed with the Dunn test. The asterisk indicates the significant difference between before intake and 6w.

☆ $P < 0.1$, ** $P < 0.01$, *$P < 0.05$.

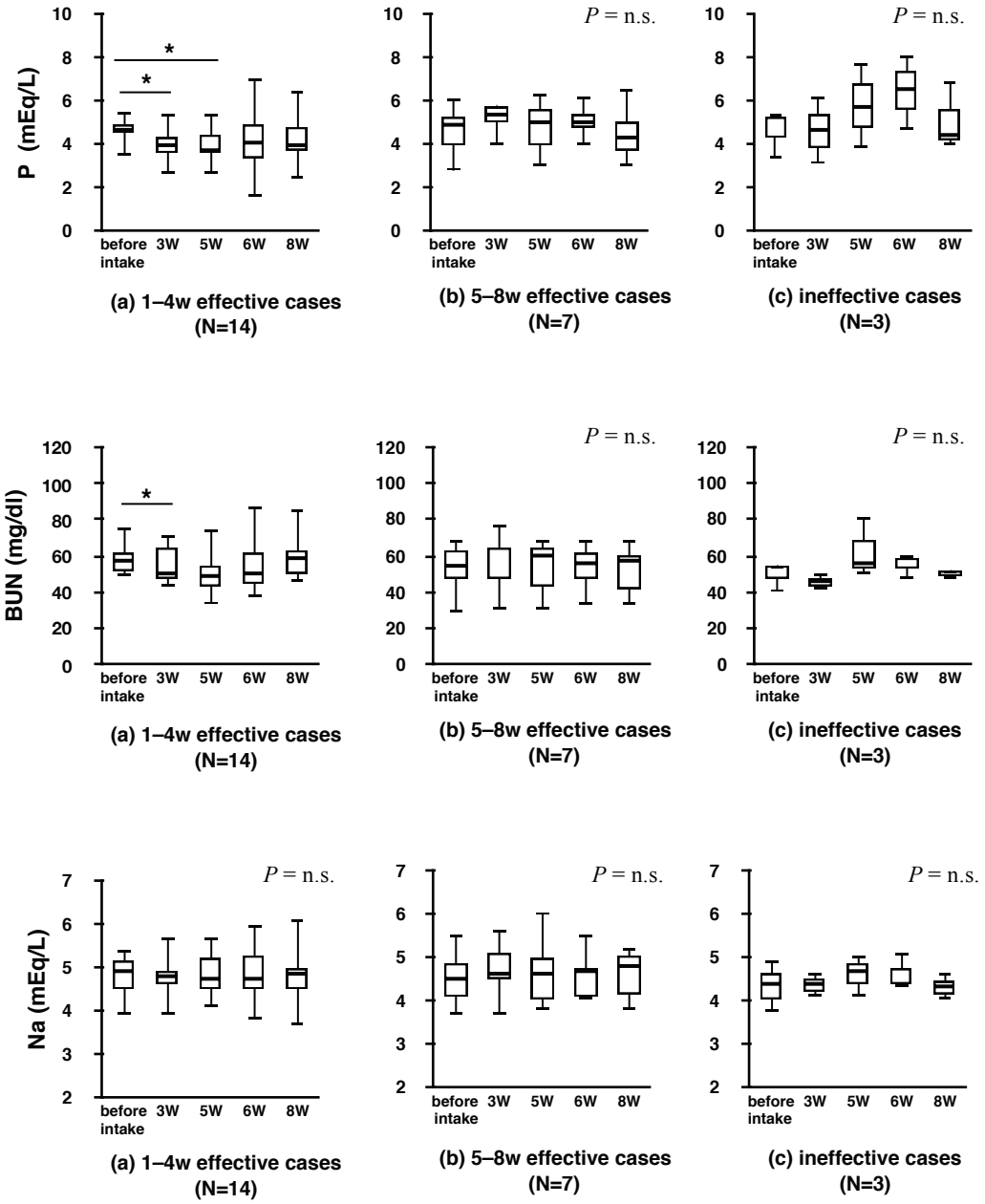


Figure 4.4 Laboratory parameters during the study

P, phosphorus; BUN, blood urea nitrogen; Na, serum sodium concentration.
Data are shown as median changes with interquartile range. Number of subjects: 1–4w effective cases (N=14); 5–8w effective cases (N=7); ineffective cases (N=3). Wilcoxon singed–rank test were used for between before intake and each period. The asterisk indicates the significant difference between before intake and each period.

** $P < 0.01$, * $P < 0.05$.

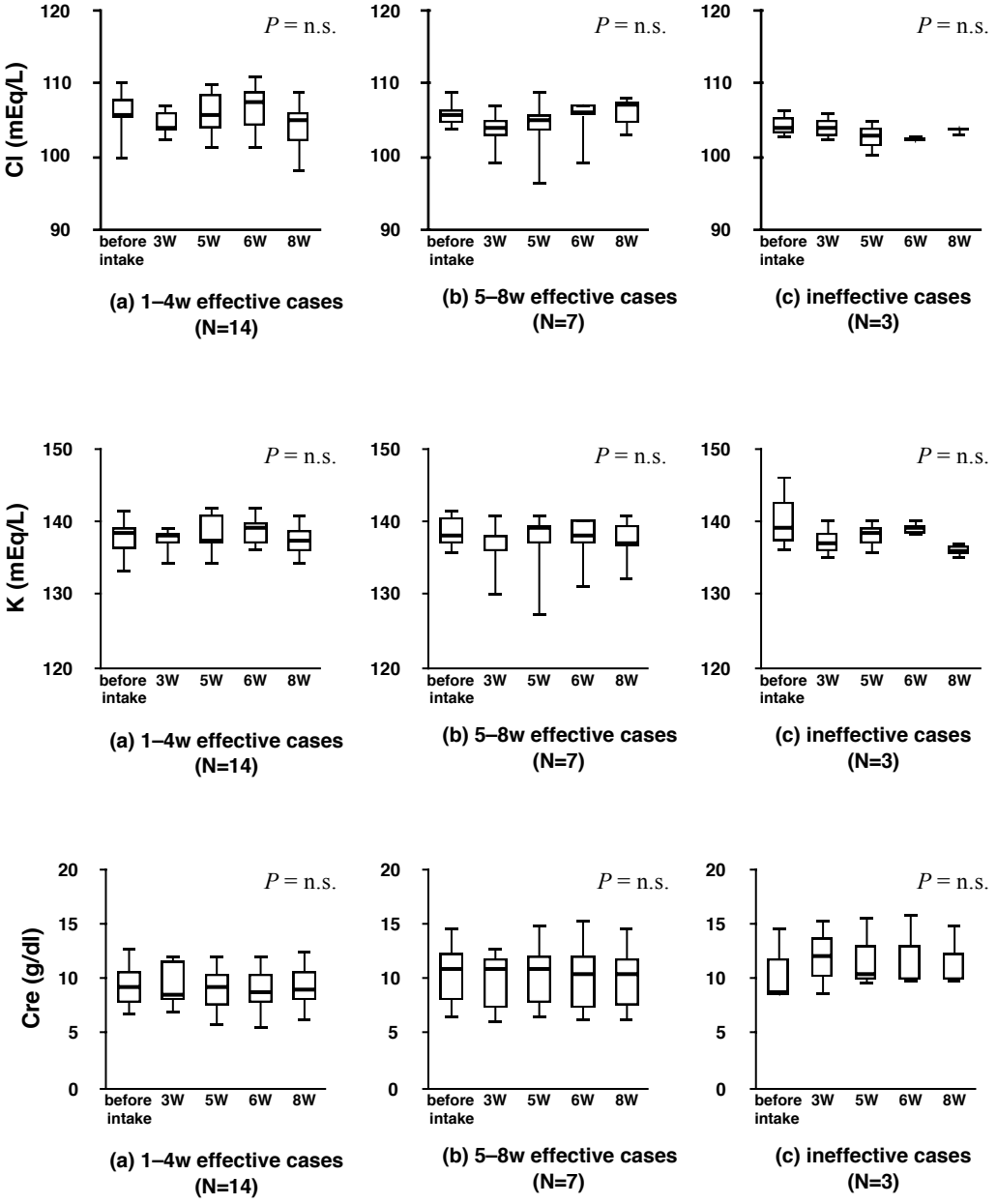


Figure 4.5 Laboratory parameters during the study

Cl, serum chloride concentration; K, serum potassium concentration; Cre, serum creatinine concentration. Data are shown as median changes with interquartile range. Number of subjects: 1–4w effective cases (N=14); 5–8w effective cases (N=7); ineffective cases (N=3). Wilcoxon singed–rank test were used for between before intake and each period.

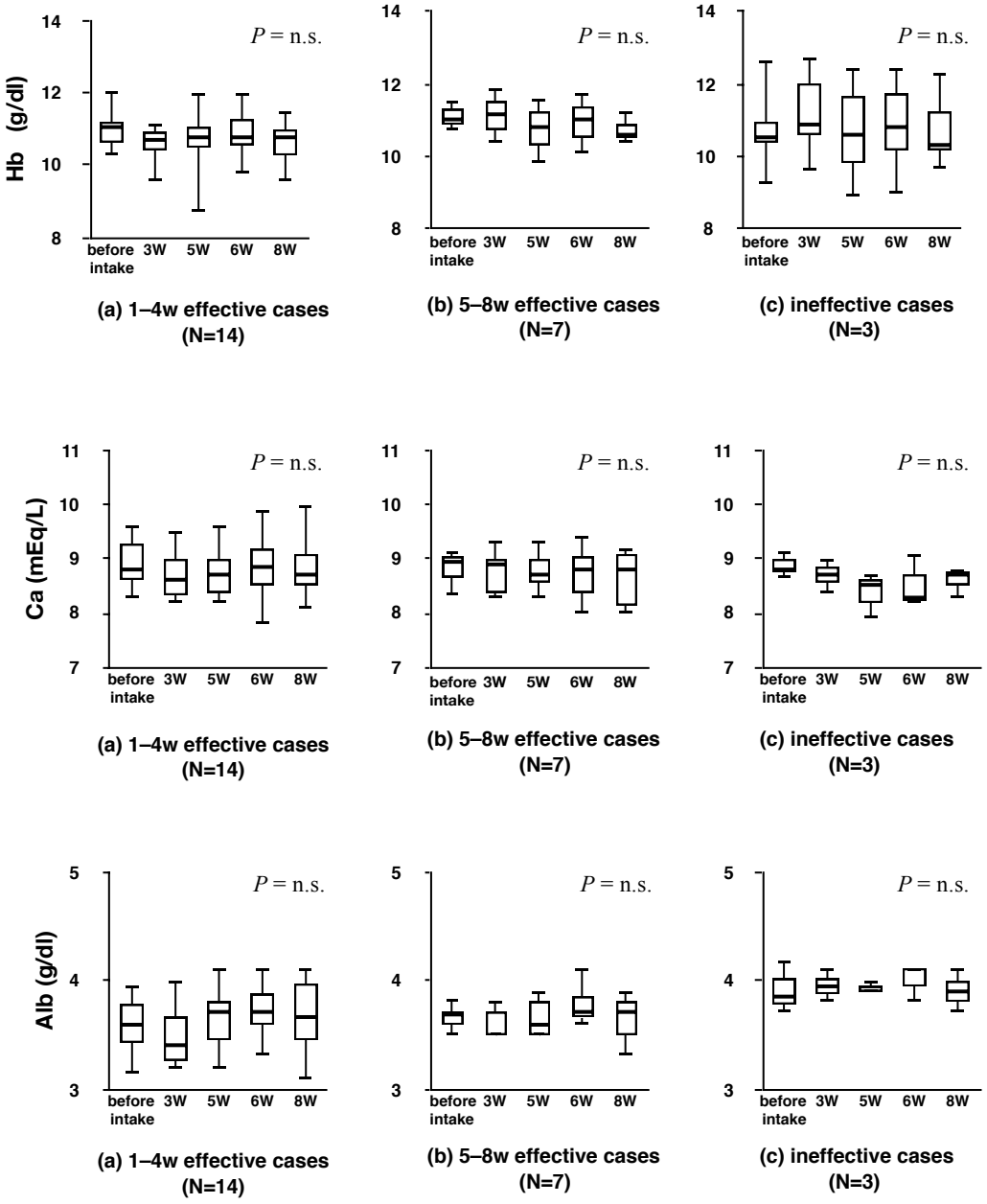


Figure 4.6 Laboratory parameters during the study

Hb, hemoglobin concentration; Ca, serum calcium concentration; Alb, serum albumin concentration. Data are shown as median changes with interquartile range. Number of subjects: 1–4w effective cases (N=14); 5–8w effective cases (N=7); ineffective cases (N=3). Wilcoxon singed–rank test were used for between before intake and each period.

4.4 Discussion

In this study, the constipation state of hemodialysis patients was evaluated, and changes in QOL associated with the improvement of constipation were assessed. Changes in blood test findings in conjunction with *Bifidobacteria*−containing enteric capsule intake were also investigated.

4.4.1 CAS

Constipation improved in 21 patients (87.5%). In 14 patients (58.3%), the CAS score fell below 5 points in 1–4 weeks, and in 7 patients (29.2%), the CAS score fell below 5 points in 5–8 weeks. *Bifidobacteria* are thought to improve constipation through the generation of lactic acid and acetic acid, causing the pH in the intestine to acidify. Consequently, the intestinal microflora is improved by suppression of aerobic bacterial growth. Previous research demonstrated the possibility of promoting Bifidobacteria propagation and inhibiting harmful bacteria such as Escherichia coli by oral administration of *Bifidobacteria* for 7−10 days [90].

In this study, of the 21 patients who experienced improvement in constipation, eight had DM and 13 did not. The three subjects in whom constipation did not improve had DM, along with mild obesity. Significant risk factors of constipation in hemodialysis patients include age, DM, and female sex [91]. DM is also associated with an increased prevalence of upper and lower gastrointestinal symptoms [92]. These three subjects experienced recurrent constipation and diarrhea prior to start of *Bifidobacteria* intake, which persisted in the same manner during the intake period. Dysbiosis, or imbalance in the composition of the bacterial microbiota including the overgrowth of potentially pathogenic bacteria and/or decrease in bacterial diversity and bacteria beneficial to the host [93], is associated with DM and a high−fat diet. It follows that the improvement of constipation by improving intestinal flora is dependent on the original enteral environment. Thus, my data suggest that the improvement of constipation was influenced by dysbiosis of the intestinal flora associated with DM or dietary habits.

4.4.2 PAC−QOL

PAC−QOL was measured in hemodialysis patients with constipation symptoms and again after improvement of constipation. In 1–4 week effective cases, the scores for physical discomfort, psychological discomfort, worries/concerns, and dissatisfaction were significantly lower after 6 weeks than before intake. In 5–8 week effective cases, the scores for physical discomfort, worries/concerns, and dissatisfaction were significantly lower after 6 weeks than before intake. In ineffective cases, the physical discomfort score was significantly lower after 6 weeks than before intake. This pattern suggests that somatic symptoms may tend to improve first, followed by psychological symptoms. In ineffective cases, the reason the score of Dissatisfaction showed low value was believed that the large influence of interviews about the constipation symptoms in every week.

In general, constipation causes not only somatic symptoms such as abdominal pain and bloating, but a humanistic burden [94]. The act of excretion is considered an activity of daily living (especially its social and psychological aspects) and behavior with psychosomatic implications. Recent studies have demonstrated that variations and changes in the composition of the intestinal flora influence normal physiology. The gut microbiota also communicate with the central nervous system and possibly influence brain function and behavior through neural, endocrine, and immune pathways [95]. The intestinal flora has been linked to both psychological and physical functions [96]. A number of studies have reported that the gut–brain axis is associated with digestive health and psychological disturbances such as depression, anxiety, and other mental health issues. Both the US and Soviet space programs have performed studies on the effects of spaceflight on microorganisms [97]. Several studies have reported that stress affects astronauts' enteric environment and have shown evidence suggestive of changes in intestinal flora. Soviet studies have reported significant reductions in Lactobacillus and *Bifidobacterium*, and significant increase in Clostridium perfringens, in crew members [98]. In a similar study, the number of Bacteroides species was markedly increased onboard Apollo and Skylab [99].

Intestinal bacterial overgrowth under stress conditions leads to the generation of harmful substances in the human intestine. Intestinal metabolism, in turn, continues to

affect the living body. Ongoing stress on the intestinal bacteria leads to reduction of *Bifidobacterium* and Lactobacillus and promotes the growth of harmful bacteria. Consequently, the risk of infectious disease expression is considered to increase. The physical stress caused by constipation causes psychological stress in hemodialysis patients. Thus, constipation may lead to a "vicious cycle" of psychosomatic sequelae.

Hemodialysis patients experience social, environmental, and temporal constraints, because hemodialysis is usually performed three of four times per week for 3 to 5 or more hours each visit. Patients are under strict dietary restrictions, and typically experience hemodialysis complications or reduction of exercise. These lifestyle restrictions significantly impact their mental and social functioning.

The present study suggests that mental health issues such as irritability can be caused by constipation. The improvement of constipation symptoms by *Bifidobacteria*−containing enteric capsules appeared to reduce physical symptoms and stress, which in turn reduced mental stress.

4.4.3 Blood test results

In 1–4 week effective cases, serum phosphorus values were significantly lower after 3 weeks and 5 weeks than before intake. In previous research, the improvement of intestinal flora was associated with decreased intestinal pH [80]. *Bifidobacteria* decreases serum phosphorus levels and lowers the pH in the intestine by improving the intestinal environment. As a result, ionized calcium is increased, and serum phosphorus is excreted as calcium phosphate rather than entering the bloodstream. In addition, The increase of *Bifidobacteria* in the intestine and their incorporation of phosphorus lead to *Bifidobacteria* excretion in the feces. Reduction of this serum phosphorus value also, since the improvement of the intestinal environment due to the improvement of defecation situation is considered, a similar mechanism is inferred. In the current study, in 1–4 week effective cases, blood urea nitrogen values were significantly lower after 3 weeks than before intake. In general, the nitrogen balance of hemodialysis patients tends to be negative due to malnutrition hypotrophy or hypermetabolism. However, recent investigations have demonstrated that *Bifidobacteria* can restrain hypermetabolism by improving enteric bacterial flora [100]. Consequently, the blood urea nitrogen values were lower after intake of *Bifidobacteria*.

4.5 Limitations of this study

This study has some limitations. The absence of a control group for a double−blind trial introduces bias, and the possibility that the improvement of constipation symptoms and the corresponding psychological changes are a result of the influence of other drugs cannot be ignored. In future studies, it will be necessary to demonstrate the performance of the *Bifidobacterium* preparation by establishing a control group. Furthermore, the patients targeted in this study were all maintenance hemodialysis outpatients, and because they prioritized the continuation of constipation relief, many chose to continue intake of the *Bifidobacterium* preparation. No crossover study was performed, in which ingestion of the *Bifidobacterium* preparation was stopped after 8 weeks, and therefore the scattering of intake effects among patients could not be controlled for. From here, it will be necessary to consider the residual effects of taking the preparation and perform a crossover study that establishes a reasonable intake cessation period. Furthermore, in this experiment, the relief of constipation symptoms was investigated only verbally, and thus it is possible that information bias arose, in which symptom relief was over− or underestimated. Relief of constipation symptoms is a product of intestinal flora and fecal decay, and it is necessary to examine the relationship between psychological changes and intestinal flora by investigating intestinal pH. Also, because there is insufficient evidence on the relationship between *Bifidobacterium* preparation and serum phosphorous levels in hemodialysis patients, the question of whether the decrease in serum phosphorous was a result of the *Bifidobacterium* preparation cannot be resolved in this study. It will be necessary to verify the relationship between intestinal pH and flora and serum phosphorous levels in hemodialysis patients.

4.6 Conclusion

Constipation can be associated with life−threatening diseases [101]. The American College of Gastroenterology Chronic Constipation Task Force defined and suggested chronic constipation as “suggest that physicians use a broad definition of chronic constipation: unsatisfactory defecation characterized by infrequent stools, difficult stool passage or both. Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool” [102]. Although many definitions of

constipation have been used, the bowel habits about constipation largely depend on the sensations of individual patients.

In the present study, constipation was significantly improved in 21 patients (87.5%) and was not improved in 3 patients (12.5%). The PAC−QOL score was significantly lower after intake of *Bifidobacterium*. Serum phosphorus levels of the group that had improved constipation at an early stage were significantly reduced compared with those before the intake of *Bifidobacterium*. Some negative psychological factors such as stress associated with hemodialysis may affect patients' chronic constipation. These results suggest that the intake of *Bifidobacterium* is useful to improve the intestinal environment and QOL of hemodialysis patients, and to reduce serum phosphorus concentration. Intake of *Bifidobacterium* may hold promise as a complementary therapy to conventional therapeutic approaches for constipation in hemodialysis patients. The author believes that additional research is needed, including the exploration of biomarkers of salivary cortisol to evaluate stress levels and the inclusion of HRV as a marker of sympathetic nervous activity to develop psychological interventions for constipation.

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Conflict of interest: The author declares no competing financial interests.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Yodogawa Christian Hospital.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Chapter V

Conclusions

Concluding Remarks

The research described in this thesis was conducted in an attempt to explore the autonomic nervous activity in patients undergoing hemodialysis. A variety of physical and psychological complications can occur over the complex course of hemodialysis treatment. Thus, not only the primary disease that led to hemodialysis, but also a variety of other disorders can become poor prognosis factors for psychological concerns. Autonomic dysfunction is the leading cause of psychologically unstable states such as depression. Therefore, better understanding the autonomic nervous activity and psychological states specific to hemodialysis patients is considered a key to improving dialysis therapy. The results described in chapter II suggest that dialysis patients with diabetic nephropathy have a tendency to experience depression and that their autonomic nervous system function is affected by hemodialysis. The results described in Chapter III indicate that high UFR is associated with an increase in sympathetic nervous overactivity and suggest that hemodialysis be performed at a UFR < 15 ml/h/kg. High UFR is a risk factor for mortality and associated with myocardial injury among hemodialysis patients. However, UFR is modifiable in hemodialysis sessions in accordance with patient conditions such as underlying disease, duration of hemodialysis, interdialytic weight gain, body weight, dialysis treatment time, and psychological factors. Further prospective studies are needed to confirm the advantages of adopting a UFR below this threshold. Additional studies are also needed in order to clarify the applicability of various techniques to specific populations of hemodialysis patients. Finally, as described in the final chapter, improving the intestinal environment, and consequently constipation, reduced serum phosphorus levels and improved the QOL of hemodialysis patients. These results may be beneficial with regard to risk factor reduction in daily life among patients receiving hemodialysis treatment.

The information relevant to the early prediction of prognosis, such as hemodialysis complications, is still incompletely understood. However, the author believes that the therapeutic approach to hemodialysis patients should consider not only a patient's physical condition but also comprehensive factors including their stress level as well as psychosomatic, psychological, and social aspects. At the time of writing this dissertation, there is a possibility that poor QOL is associated with increased mortality in hemodialysis patients. Thus, further research is necessary to assess not only the dialysis technique, but also the psychological aspects of care. Improved physical function leading to improved mental health in the context of constipation, but they do

not appear to support causality in the direction stated here. Therefore, the author recognizes that the ongoing refinement of hemodialysis treatment to maintain patients' psychological and physical suitably for their environment. In the near future, the author is planning an investigation of a psychological and physical condition guidance system by measuring the change in HRV in a clinical setting.

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