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### 学位論文の要旨

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.

## 論文審査の結果の要旨

本論文は、血液透析患者の自律神経反応を生理心理学的観点から評価したものである。血液透析患者は、慢性腎臓病に関する多くの合併症を抱え、肉体的および心理的な問題を有している。血液透析患者において観察される最も重篤な合併症の一つに自律神経機能障害があり、自律神経機能障害は、うつ病など心理的不安定要素の一つである。

第2章では、血液透析における体外循環と血液透析に対する心身症状や不安状態が慢性腎臓病患者の自律神経機能に与える影響を指尖容積脈波と心理検査を用いて検討した。本研究では、血液透析開始直後から糖尿病性腎症患者の心拍変動の不安定性が認められ、糖尿病性腎症患者の自律神経活動は、交感神経活動と副交感神経活動の相対的な活動が破綻していることが推測された。また、糖尿病性腎症患者は心理的に問題がみられ、糖尿病性腎症患者の自律神経機能異常は、体外循環という外因的影響のみではなく、心理的・情動的要因の影響を受け増強しているという知見を得た。

第3章では、限外濾過率 (ultrafiltration rate: UFR) の違いによる自律神経活動の経時的変化を心拍変動と Approximate entropy を用いて定量化したものである。本研究では、UFR が 15 ml/min/ kg を超える血液透析では血液透析中の血圧に変化がない場合においても、血液透析後半では交感神経の過活動と副交感神経活動の低下が認められた。交感神経の過活動は血液透析中の致死性不整脈や心臓突然死を引き起こす原因の一つであることから、血液透析中の血圧変動がない場合においても、UFR は 15 ml/min/ kg 未満で行うべきであるという知見を得た。

第4章では、血液透析患者の脳腸相関の観点から、腸溶性ビフィズス菌製剤を用いて血液透析患者の便秘症状とそれに伴う心理変化を検討した。本研究では、腸溶性ビフィズス菌製剤の効果が早期に出現する血液透析患者では、便秘症状の改善に伴う QOL (quality of life) の改善および血清リン値の低下に有用であることが示唆された。便秘症状の改善は血液透析患者の負の情動感情を軽減させ、QOL を向上させることが可能であるという知見を得た。

本研究により、血液透析患者に特異的な自律神経活動と心理状態を定量・認識し、これらの管理手法が血液透析患者のリスクを軽減するために有用であることが示された。これらは、今後の透析医療に発展につながる意義の高い知見であると考えられる。

以上を総合して本審査委員会は、本論文が博士 (応用情報科学) の学位授与に値するものと全員一致で判断した。