Icodextrin-Based Continuous Ambulatory Peritoneal Dialysis Therapy Effectively Reduces Left Ventricular Mass Index and Protects Cardiac Function in Patients with End-Stage Renal Disease

Increased left ventricular mass index (LVMI) is commonly observed in patients undergoing peritoneal dialysis (PD). The present study aimed to determine the effect of icodextrin (Ico) on LVMI in PD patients with maintained residual renal function (RRF).

This retrospective study included 18 patients (12 men, 6 women; average age: 62 ± 10 years) diagnosed with indications for PD therapy and divided into two groups: those treated with Ico (Ico group) and without Ico (non-Ico group). Echocardiography was performed at the beginning of continuous ambulatory PD and after 6 and 12 months.

A significant reduction in LVMI ($p < 0.01$) and an increase in ultrafiltration ($p < 0.01$) were observed after 6 months of Ico treatment and were maintained for 12 months. Ejection fraction was significantly lower in the non-Ico group after 12 months ($p < 0.01$), but was not altered in the Ico group. Blood pressure, cardiothoracic ratio, urine volume, and N-terminal prohormone of brain natriuretic peptide were unaffected by PD treatment up to 12 months. The year-averaged ultrafiltration and the reduction in LVMI were significantly correlated ($p < 0.05$).

Ico effectively improved LVMI and maintained ejection fraction in end-stage renal disease patients within 1 year from PD initiation. Notably, treatment with Ico resulted in a reduction of LVMI (associated with increased ultrafiltration), with no significant reduction in RRF.

Key words
Icodextrin, residual renal function, left ventricular mass index

Introduction
The incidences of cardiovascular disease and cardiovascular mortality are both higher in patients with end-stage renal disease (1). Left ventricular hypertrophy (LVH), which is easily measured by echocardiography, is commonly observed in patients with end-stage renal disease and is a major predictor of cardiovascular death (2,3).

Volume overload is commonly observed in patients receiving long-term peritoneal dialysis (PD) and plays a role in the reduction of cardiac function. Takeda et al. (4) reported that, compared with hemodialysis (HD) patients or patients on PD for less than 5 years, those with a PD duration of 5 years or more had higher blood pressure and a greater left ventricular mass index (LVMI). Icodextrin (Ico)—based peritoneal dialysate, widely used in PD for gradual ultrafiltration, is free from glucose toxicity (5). Although Ico increases ultrafiltration volume compared with conventional 2.5% glucose PD solution, residual renal function (RRF) is maintained (6).
We hypothesized that Ico may play a beneficial role for LVH in PD patients without loss of RRF. We tested that hypothesis by analyzing LVH and urine volume retrospectively for 1 year in Japanese PD patients who were treated with or without Ico.

**Methods**

Patients who met all the following criteria were included in this retrospective study:

- Started on PD between April 2008 and January 2010
- Average daily urine volume of 800 mL or more during follow-up
- Cardiac function monitored by echocardiography for more than 1 year

Table I presents the year-averaged clinical parameters for the study subjects. The patients were divided into two groups: those treated with Ico [Extraneal: Baxter Healthcare, Tokyo, Japan (Ico group)] or without Ico (non-Ico group). All human study protocols were approved by the institutional ethics committee.

Blood samples were collected for measurement of chemical parameters at monthly follow-up visits starting with the first outpatient visit (within 1 month of PD start). The N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was measured once every 3 months. Two-dimensional echocardiography was performed at the beginning of PD and after 6 and 12 months of treatment. The Devereux formula was used to obtain LVMI (7), and a modified version of the biplane Simpson method was used to obtain LVEF.

Statistical analyses were performed using the Sigma Plot software (version 11.0: SPSS, Chicago, IL, U.S.A.). Comparisons of clinical parameters between the Ico and non-Ico groups were performed using the Student t-test. One-way ANOVA was used to evaluate changes in LVMI, ejection fraction (EF), ultrafiltration, and urine volume. Associations between EF and LVMI, and between ultrafiltration and LVMI were evaluated using linear regression analysis. A p value less than 0.05 was considered to be statistically significant.

**Results**

**Baseline characteristics and clinical parameters**

The study enrolled 18 PD patients (12 men, 6 women). Table I summarizes their baseline characteristics and clinical parameters. Indicators of volume overload such as blood pressure, cardiothoracic ratio, urine volume, and ultrafiltration were similar in both groups. Anemia and use of erythropoiesis-stimulating agents were similar in both groups. Ejection fraction was significantly lower in the Ico group than in the non-Ico group (p < 0.05). No cardiovascular events or deaths occurred during the study.

**Changes in LVMI and cardiac function after Ico treatment**

Left ventricular mass index remained unchanged throughout the 1-year follow-up in the non-Ico group [Figure 1(A)]. In contrast, LVMI declined significantly in the Ico group after treatment for 6 months, and the level achieved was maintained for 1 year [Figure 1(A)]. Baseline LVMI was significantly
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higher in the Ico group, and so subjects with a LVMI of 80 – 130 g/m² in the two group were selected and compared [Figure 1(B); non-Ico group, n = 6; Ico group, n = 8]. In this subanalysis, baseline LVMI was similar in both groups. In the Ico group, a significant reduction in LVMI was observed after 6 months and was maintained for 1 year; in the non-Ico group, no significant reduction was observed. As shown in Figure 1(C), a significant reduction in EF was observed in the non-Ico group after 1 year; in contrast, EF was maintained in the Ico group [Figure 1(C)]. To examine the role of LVMI in cardiac function, we analyzed the correlation between LVMI and EF. We observed a significant correlation between LVMI and EF, indicating that the reduction in LVMI was responsible for preserving cardiac function [Figure 1(F)]. The E/E′ and the level of NT-proBNP did not change throughout the study in either group.

Changes in volume status after Ico treatment
After 6 months of Ico treatment, ultrafiltration was significantly increased, and it was maintained for 1 year. No significant change was observed in the non-Ico group [Figure 1(D)]. No changes in urine volume were seen throughout the study in either group [Figure 1(E)].

To determine if volume overload was responsible for the reduction in LVMI, we examined the correlation between ultrafiltration and LVMI [Figure 1(G)]. We observed a significant correlation between ultrafiltration and LVMI, indicating that improved ultrafiltration might be responsible for the reduction in LVMI.

Discussion
The present study investigated the ability of Ico to improve LVMI without reducing RRF. After 6 months of Ico treatment, LVMI was significantly improved, followed by EF after 1 year. Although the precise mechanism responsible for this reduction in LVMI remains unknown, reduction in volume overload might be a contributory factor, because ultrafiltration was increased in the Ico group, but not in the non-Ico group. In addition, improvements in ultrafiltration and EF were significantly correlated with the reduction in LVMI, indicating that volume reduction through Ico treatment reduced LVMI, thereby improving EF. Wang et al. (7) demonstrated that a 1 g/m² increase in LVMI significantly predicts heart failure during 4 years of follow-up (hazard ratio: 1.005) in patients without a prior history of heart failure. Thus, in the present study, the reduction of LVMI with the use of icodextrin might involve preservation of EF. To the best of our knowledge, the present study is the first to demonstrate, in a Japanese population, that Ico might significantly reduce LVMI and preserve EF in patients with maintained RRF.

Reduction of LVMI by Ico in PD patients with maintained RRF
Cardiac function has been shown to decline in patients receiving PD for 5 or more years compared with patients receiving HD (4). That finding might be explained by the volume overload associated with PD. In continuous ambulatory PD patients, LVH is also a strong predictor of cardiovascular morbidity and mortality (8). Because Ico has been used in PD patients to achieve better ultrafiltration than is achieved with conventional glucose-based dialysis solutions, its beneficial effect on LVMI has been investigated in several studies.

Reduced LVMI was observed after 3 months of Ico treatment in PD patients with reduced or no RRF (8). Wang et al. (9) found a cross-sectional relationship between RRF and LVH in nondiabetic end-stage renal disease patients on PD. However, no studies have determined the effect of Ico on LVH and RRF in a Japanese population. The present study confirmed that Ico could also reduce LVMI in Japanese PD patients with maintained RRF.

Left ventricular hypertrophy has also been shown to be associated with cardiac dysfunction and mortality. In the present study, EF declined after 6 months of increased left ventricular mass, indicating that left ventricular mass was responsible for cardiac dysfunction. Because PD patients tend to be more overhydrated than HD patients, left ventricular mass is also likely to be higher in PD patients than in HD patients (4). However, Gunal et al. (10) showed that, in patients on continuous ambulatory PD and HD with normal volume status and blood pressure, cardiac structure and function were similar. The foregoing results suggest that the Ico-induced increase in ultrafiltration may improve volume status and thereby improve cardiac structure and function, as indicated by LVMI and EF in the present study.

Mechanisms involved in reduction of LVMI by Ico
Reduced LVMI was associated with increased ultrafiltration. Other parameters that may have influenced
LVMI, such as blood pressure or NT-ProBNP, were similar in the two groups. As in the present study, Konings et al. (5) observed that Ico significantly increased ultrafiltration and improved LVMI, associated with a reduction in extracellular volume (determined by the bromide dilution method), revealing that volume overload induced by inadequate ultrafiltration might be responsible for the increase in LVMI in PD patients.
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Maintained RRF by Ico treatment
Although Ico results in strong ultrafiltration, RRF can be maintained, as shown in the present study. In a meta-analysis of nine randomized controlled trials, Qi et al. examined the safety and efficacy of Ico (11). The results of the meta-analysis indicate that, compared with conventional glucose solutions, Ico has the advantages of greater ultrafiltration and small-solute clearance. Despite strong fluid removal, Ico maintained RRF, as it did in the present study.

Study limitations
The present study has several limitations. First, baseline EF was significantly lower in the Ico group, which might have contributed to the increased baseline volume overload in the Ico group. Further analyses of volume status, such as those using body composition measures, are required. Baseline LVMI was also higher in the Ico group, and although we performed subanalyses to match the groups, prospective studies are still needed to verify the results. Second, maintenance of RRF in the present study was estimated using only urine volume; other parameters such as small-solute removal should also be determined. Third, although several other studies have demonstrated that increased left ventricular mass is associated with mortality (2,9,10), the extent to which reduction of LVMI by Ico improves mortality in PD patients has not been evaluated and should be investigated in future studies.

Conclusions
In PD, Ico is useful for maintaining LVMI (especially in patients with higher LVMI) and EF without altering RRF in patients with relatively conserved RRF.

Disclosures
The authors have no financial conflicts of interest to disclose.

References

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