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Left atrial volume is an independent predictor of mortality in CAPD patients

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Abstract

Background. Echocardiography is an established technique to estimate the risk for cardiovascular complications in patients with end-stage renal disease (ESRD). An enlarged left atrium (LA) has recently emerged as a marker of adverse cardiovascular outcomes in various pathologic conditions. However, there have been few studies to evaluate its prognostic value in patients with ESRD, particularly those receiving continuous ambulatory peritoneal dialysis (CAPD).

Methods. We conducted an observational cohort study to investigate whether enlarged LA can predict patient outcome in 216 patients with CAPD. Study outcomes were all-cause and cardiovascular mortality.

Results. Increased left atrium volume index (LAVI > 32 mL/m^2) was observed in 99 (45.8%) of the CAPD patients. During the follow-up (26.3 $\pm$ 18.6 months), 20 patients (9.3%) died. Kaplan–Meier analysis revealed that the 5-year survival rate was significantly lower in patients with LAVI > 32 mL/m^2 than those with LAVI ≤ 32 mL/m^2 (69 versus 82%, $P = 0.024$). In multivariate analyses adjusted for echocardiographic parameters and clinical and laboratory data, increased LAVI was an independent predictor of all-cause mortality [hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.01–1.10, $P = 0.03$] and cardiovascular mortality (HR 1.08, 95% CI 1.02–1.14, $P = 0.006$). Furthermore, increased LAVI provided the highest predictive value for all-cause mortality [area under the receiver operating characteristic curve (AUC) $= 0.766$, $P < 0.001$] and cardiovascular mortality (AUC $= 0.836$, $P < 0.001$) among the measured echocardiographic parameters.

Conclusions. We showed that increased LAVI predicted adverse outcomes better than other echocardiographic parameters in patients with CAPD.

Keywords: CAPD; echocardiography; left atrial volume; mortality

Introduction

Echocardiography is an established technique used to estimate the risk for cardiovascular complications and to guide treatment in patients with end-stage renal disease (ESRD) [1]. Among the many parameters measured by this technique, left ventricular mass index (LVMI), ejection fraction

(EF) and LV chamber volume are particularly helpful in initial risk stratification and risk monitoring in the follow-up of dialysis patients [2].

Recently, an enlarged left atrium (LA) has emerged as another valuable parameter to predict adverse cardiovascular outcomes. In general, the LA serves multiple functions, acting as a reservoir during LV systole, a conduit for blood transiting from the pulmonary veins to the LV during early diastole, an active contractile chamber that augments LV filling in late diastole and a suction source that refills itself in early systole [3]. The LA enlarges in response to two broad conditions: pressure and volume overload. LA enlargement due to pressure overload is usually secondary to increased LA afterload in mitral valve disease or LV dysfunction. Chronic volume overload associated with conditions such as valvular regurgitation, arteriovenous fistula and high output states including chronic anemia and athletic heart can also contribute to chamber enlargement [4]. Such an enlarged LA is reported to predict adverse cardiovascular outcomes such as atrial fibrillation, stroke, congestive heart failure and cardiovascular death in the general population [4].

In patients undergoing peritoneal dialysis (PD), enlarged LA volume is commonly observed because they have chronic volume overload and increased afterload due to LV hypertrophy [5]. However, there have been few studies to evaluate the prognostic value of this parameter in patients with ESRD, particularly those receiving continuous ambulatory peritoneal dialysis (CAPD). We conducted this observational cohort study to investigate whether enlarged LA can predict patients' adverse outcomes and to compare its predictive usefulness with other echocardiographic parameters in these patients.

Materials and methods

Patients

A total of 344 patients started CAPD at Yonsei University Medical Center between January 2005 and July 2010. Twenty-eight patients who did not perform the evaluation of baseline cardiac function due to non-compliance, cost issue or other personal reasons were excluded. Of the remaining 316 patients, 297 patients underwent echocardiography, whereas other types of cardiac evaluation such as nuclear imaging were conducted in 19 patients. We further screened 262 patients who underwent echocardiography within 1 month after the initiation of CAPD for the eligibility of the study excluding 35 patients in whom echocardiography was performed after this period or before the initiation of CAPD. Of these patients, the exclusion of 46 patients occurred for the following reasons: PD duration <3 months ($n = 8$), patients <20 ($n = 2$) or >75 years of age ($n = 8$), hemodialysis or kidney transplantation before the initiation of PD ($n = 3$), severe systolic dysfunction (EF $< 30\%$, $n = 12$), severe mitral stenosis or regurgitation ($n = 4$), underlying malignancy ($n = 6$), decompensated liver cirrhosis ($n = 2$) and immunosuppressive therapy due to systemic lupus erythematosus ($n = 1$). Thus, a total of 216 patients were included in the final analysis. Patients were categorized as icodextrin users if patients used this solution for >6 months during the study period.

Data collection

At the initiation of PD, patients' demographic and clinical data such as age, gender and comorbid conditions were recorded. In addition, laboratory parameters such as hemoglobin serum albumin, blood urea nitrogen, creatinine, calcium, phosphorus and intact parathyroid hormone were measured at that time. C-reactive protein (CRP) was measured by laser nephelometry (IMMAGE; Beckman Coulter, Brea, CA). A peritoneal equilibrium test (PET) was conducted and dialysis adequacy and residual renal function (RRF) were measured within 2 months after the initiation of CAPD. Equilibration ratios were measured in a standardized PET that involved a 2-L 4.25% dextrose dwell with dialyzate samples taken at 0, 2 and 4 h and a plasma sample at 2 h. According to their 4-h dialyzate-to-plasma ratio (D/P) for creatinine, patients were categorized as one of the following four peritoneal transport types: high (above +1 SD from the mean), high average (between the mean and +1 SD), low average (between the mean and −1 SD) or low (below −1 SD from mean) [6]. Drained dialyzate and 24-h urine (if residual renal function was present) were collected within 1 day before the PET. Creatinine and urea nitrogen were measured in blood, urine and drained dialyzate. The residual glomerular filtration rate was calculated as the mean of urinary creatinine and urea clearances standardized to 1.73 m^2 body surface area (BSA). Weekly Kt/V urea was calculated as the ratio of urinary and 24-h dialyzate urea clearance to total body water [7].

Echocardiography

Echocardiographic examinations were performed using an imaging protocol according to the American Society of Echocardiography recommendations [8]. This study was performed with an empty abdomen in CAPD patients. Standard echocardiography analysis included two dimensional, M-mode and Doppler flow measurements, using a SONOS 7500 (Philips Ultrasound, Bothell, WA). The LV systolic function was determined by the LV EF using a modified biplane Simpson's method from apical two- and four-chamber views [9] and systolic dysfunction was defined as EF $<$ 55%. The LV mass was calculated by the method described by Devereux and Reichek [10]. The LVMI was calculated by dividing LV mass to BSA, and LV hypertrophy was defined as a LVMI > 131 g/m^2 for men and >100 g/m^2 for women [11]. The LA volume was assessed by the biplane area–length method from apical four-chamber and two-chamber views [12]. Measurements were obtained in end systole from the frame preceding mitral valve opening, and the LA volume was indexed for BSA. According to population-based studies, a value of 32 mL/m^2 was considered as the upper limit of a normal LAVI [13]. Mitral inflow was assessed with pulse-wave Doppler echocardiography from the apical four-chamber view. The Doppler beam was aligned parallel to the direction of flow, and a 1- to 2-mm sample volume was placed between the tips of the mitral leaflets during diastole. From the mitral inflow profile, peak E-wave velocity and its deceleration time, peak A-wave velocity and the isovolumetric relaxation time were measured [14]. Doppler tissue imaging of the mitral annulus was also obtained. From the apical four-chamber view, a 1- to 2-mm sample volume was placed in the septal mitral annulus. The early mitral inflow velocity to peak mitral annulus velocity (E/E′) ratio >15 was regarded as an abnormally elevated LV filling pressure [15]. Systolic right ventricular pressure (RVP) was calculated using the modified Bernoulli equation [$4 \times$ (tricuspid systolic jet)^2 + 10 mmHg], and pulmonary arterial hypertension was defined as RVP $>$ 35 mmHg at rest [16].

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Continuous data were expressed as mean ± SD, and categorical data were expressed as a number (percentage). Comparisons between the two groups were done by *t*-test or chi-squared test. The relationship between paired variables was analyzed using the Pearson sample correlation coefficient. Cumulative survival curves were generated by the Kaplan–Meier method, and between-group survival was compared by the log-rank test. In this analysis, patients who underwent a kidney transplant or were transferred to hemodialysis during follow-up were censored at the time of transfer to alternative renal replacement therapy. If a patient died within 3 months of transfer to hemodialysis, then he or she was not censored because the early mortality was considered to reflect the patient's health status during the period of failing PD treatment. The independent prognostic value of LAVI for all-cause and cardiovascular (CV) mortality was analyzed by multiple Cox regression analysis. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated with the use of the estimated regression coefficients and standard errors in the Cox regression analysis. The predictive value for all-cause and CV mortality was analyzed by receiver operating characteristic (ROC) curve analysis with calculated area under the ROC curve (AUC). All probabilities were two tailed and the level of significance was set at 0.05.

Results

Baseline characteristics of patients

The baseline characteristics of the study population are shown in Table 1. Of the 216 patients, 99 patients

Table 1. Demographic, clinical and biochemical characteristics[a]

	LAVI $\leq$ 32 mL/m^2 (n = 117)	LAVI > 32 mL/m^2 (n = 99)	P-value
Age (years)	55.3 ± 13.9	59.8 ± 11.7	0.011
Gender (male, *n*) (%)	61 (52.1%)	60 (60.6%)	NS
Body surface area (m^2)	1.6 ± 0.2	1.7 ± 0.2	NS
Diabetes (*n*, %)	45 (38.5%)	48 (48.5%)	NS
Coronary arterial disease (*n*, %)	16 (13.7%)	19 (19.2%)	NS
Hypertension (*n*, %)	89 (76.1%)	79 (79.8%)	NS
Systolic blood pressure (mmHg)	135.7 ± 16.9	145.6 ± 18.9	<0.001
Diastolic blood pressure (mmHg)	80.7 ± 11.4	78.7 ± 11.8	NS
Medications use (*n*, %)			
ACE inhibitors or ARBs	74 (63.2%)	63 (63.6%)	NS
HMG-CoA reductase inhibitors	33 (28.2%)	31 (31.3%)	NS
Oral active vitamin D	17 (14.5%)	12 (12.1%)	NS
Duration of dialysis (months)	28.3 ± 19.4	23.8 ± 17.3	NS
Use of icodextrin (*n*, %)	36 (30.8%)	32 (32.3%)	NS
Baseline RRF (mL/min/1.73 m^2)[b]	3.9 ± 3.5	3.6 ± 2.6	NS
Urine volume (mL)[b]	743.1 ± 578.9	761.8 ± 609.8	NS
Weekly Kt/V[b]	2.4 ± 0.6	2.3 ± 0.6	NS
Peritoneal Kt/V[b]	1.6 ± 0.4	1.6 ± 0.3	NS
Renal Kt/V[b]	0.8 ± 0.6	0.7 ± 0.5	NS
High and HA transporter (*n*, %)[b]	61 (71.8%)	52 (77.6%)	NS
CRP (mg/L)	1.2 ± 1.8	1.3 ± 2.0	NS
Blood urea nitrogen (mg/dL)	67.7 ± 23.9	69.3 ± 31.3	NS
Creatinine (mg/dL)	7.7 ± 2.6	7.4 ± 3.0	NS
Albumin (g/dL)	3.6 ± 0.6	3.4 ± 0.6	0.048
Hemoglobin (g/dL)	9.3 ± 1.4	8.7 ± 1.4	0.003
Calcium (mg/dL)	8.3 ± 0.8	8.0 ± 0.8	0.016
Phosphate (mg/dL)	5.5 ± 1.3	5.5 ± 1.4	NS
Parathyroid hormone (pg/mL)	176.4 ± 164.2	167.8 ± 130.6	NS

[a]ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; RRF, residual renal function; Kt/V, urea clearance; NS, not significant. Data are presented as *n* (%) or mean ± SD.
[b]Dialysis adequacy, RRF and PET were measured in 97 patients with LAVI $\leq$ 32 mL/m^2 and in 77 with LAVI > 32 mL/m^2.

(45.8%) had LAVI > 32 mL/m^2 and were considered to have enlarged LA volume. Compared to patients with LAVI $\leq$ 32 mL/m^2, those with LAVI > 32 mL/m^2 were older (55.3 ± 13.9 versus 59.8 ± 11.7 years, P = 0.011) and had higher systolic blood pressure (135.7 ± 16.9 versus 145.6 ± 18.9 mmHg, P < 0.001). In addition, albumin (3.6 ± 0.6 versus 3.4 ± 0.6 g/dL, P = 0.048) and hemoglobin (9.3 ± 1.4 versus 8.7 ± 1.4 g/dL, P = 0.003) levels were significantly lower in patients with LA dilatation. There were no differences in comorbidities, medications, serum CRP levels, use of icodextrin, peritoneal membrane permeability, dialysis adequacy and residual renal function between the two groups (Table 1).

Compared to patients with low/low average (L/LA) transporters, serum albumin level (3.7 ± 0.6 versus 3.5 ± 0.6 g/dL, P = 0.031) was significantly lower in those with high/high average (H/HA) transporters, whereas LAVI, blood pressure and the proportion of icodextrin users were not different between the two groups (data not shown).

Echocardiographic findings

The differences in echocardiographic parameters between the two groups of patients are presented in Table 2. LV end-diastolic diameter (49.5 ± 5.1 versus 55.0 ± 6.4 mm, P < 0.001), LVMI (118.6 ± 31.9 versus 152.7 ± 37.4 g/m^2, P < 0.001), RVP, 27.8 ± 8.4 versus 35.2 ± 11.3 mmHg, P < 0.001) and the early mitral inflow velocity to peak mitral annulus velocity (E/E′) ratio (12.3 ± 4.7 versus 18.8 ± 8.2, P < 0.001) were elevated in patients with LAVI > 32 mL/m^2, while there was no difference in EF between the two groups. LAVI was positively correlated with LVMI (r = 0.636, P < 0.001), RVP (r = 0.425, P < 0.001) and E/E′ ratio (r = 0.542, P < 0.001), whereas it was inversely correlated with EF (r = −0.189, P = 0.005) (Figure 1).

Predictors of mortality

During the mean follow-up duration of 26.3 ± 18.6 (3.0 – 69.5) months, 20 patients (9.3%) died, 75% of them from cardiovascular causes including sudden cardiac death, acute myocardial infarction or fatal arrhythmias. The 5-year survival rate was significantly lower in patients with LAVI > 32 mL/m^2 than those with LAVI $\leq$ 32 mL/m^2 (69 versus 82%, P = 0.024) (Figure 2). In addition, patients with LV systolic dysfunction (EF < 55 versus ≥ 55%, P = 0.017), pulmonary hypertension (RVP > 35 mmHg versus ≤ 35 mmHg, P = 0.021) and LV diastolic dysfunction (E/E′ ratio >15 versus ≤15, P = 0.014) had a higher

mortality. However, survival was not different between patients with H/HA transporters and those with L/LA transporters (log-rank test, P = 0.26).

Multivariate analysis adjusted for echocardiographic parameters, diabetes, history of coronary arterial disease, CRP, serum albumin and hemoglobin showed that increased LAVI was an independent predictor of all-cause (HR 1.05, 95% CI 1.01–1.10, P = 0.03) and cardiovascular mortality (HR 1.08, 95% CI 1.02–1.14, P = 0.006). In addition, elevated RVP (HR 1.06, 95% CI 1.00–1.13, P = 0.035), history of coronary arterial disease (HR 12.30, 95% CI 2.11–71.90, P = 0.005) and increased serum CRP concentrations (HR 1.59, 95% CI 1.20–2.12, P = 0.002) were significantly associated with an increased risk of all-cause mortality (Tables 3 and 4). Increased LAVI remained an independent predictive value for all-cause (HR 1.08, 95% CI 1.03–1.12, P = 0.001) and cardiovascular mortality (HR 1.10, 95% CI 1.05–1.15, P < 0.001) in a multivariate analysis adjusted for transport types, whereas high transport status did not have influence on mortality. Furthermore, increased LAVI provided the highest predictive value for all-cause (AUC = 0.766, P < 0.001) and cardiovascular mortality (AUC = 0.836, P < 0.001) among measured echocardiographic parameters (Figure 3).

Table 2. Echocardiographic parameters[a]

	LAVI ≤ 32 mL/m^2 (n = 117)	LAVI > 32 mL/m^2 (n = 99)	P-value
EF (%)	62.4 ± 10.0	59.5 ± 12.4	NS
LVEDD (mm)	49.5 ± 5.1	55.0 ± 6.4	<0.001
LVM (g)	195.1 ± 56.8	257.5 ± 67.7	<0.001
LVM index (g/m^2)	118.6 ± 31.9	152.7 ± 37.4	<0.001
LAV (mL)	39.2 ± 10.0	77.9 ± 23.7	<0.001
LAV index (mL/m^2)	23.8 ± 5.2	46.5 ± 14.5	<0.001
RVP (mmHg)	27.8 ± 8.4	35.2 ± 11.3	<0.001
E/E′	12.3 ± 4.7	18.8 ± 8.2	<0.001
E/A	0.9 ± 0.3	1.0 ± 0.6	0.02

[a]LVEDD, left ventricular end-diastolic diameter; LVM, left ventricular mass; LAV, left atrial volume; E/E', ratio of early mitral inflow velocity to peak mitral annulus velocity; E/A, ratio of early to late transmitral flow velocity; NS, not significant. Data are presented as mean ± SD.

Discussion

This study showed that increased LAVI was an independent risk factor for all-cause and cardiovascular mortality in CAPD patients. In addition, LV systolic dysfunction, pulmonary hypertension and abnormally elevated LV filling pressure predicted adverse outcomes in these patients. Among these echocardiographic parameters, increased LAVI provided the highest predictive value for all-cause and cardiovascular mortality.

Recently, much attention has been focused on LA volume as an indicator of CV outcomes in addition to LV

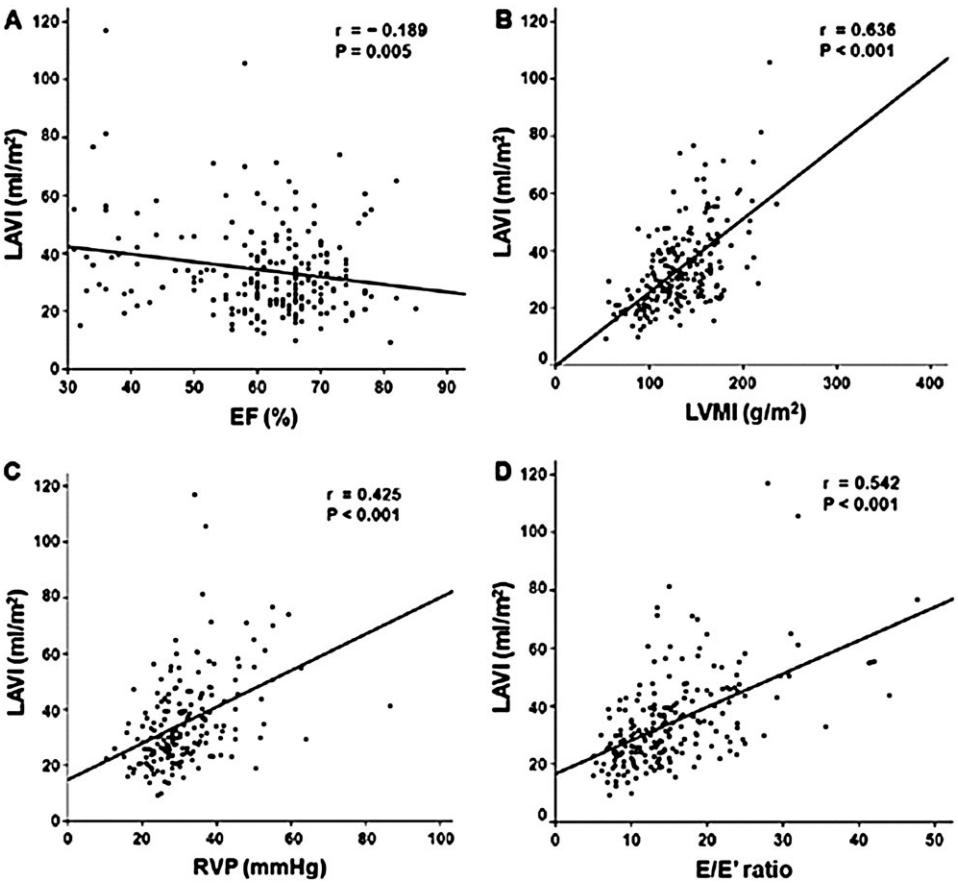

Fig. 1. Relationship between LAVI with EF (**A**), left ventricular volume index (**B**), RVP (**C**) and the early mitral inflow velocity to peak mitral annulus velocity (E/E′) ratio (**D**). Data are correlation coefficients (r) and P-values.

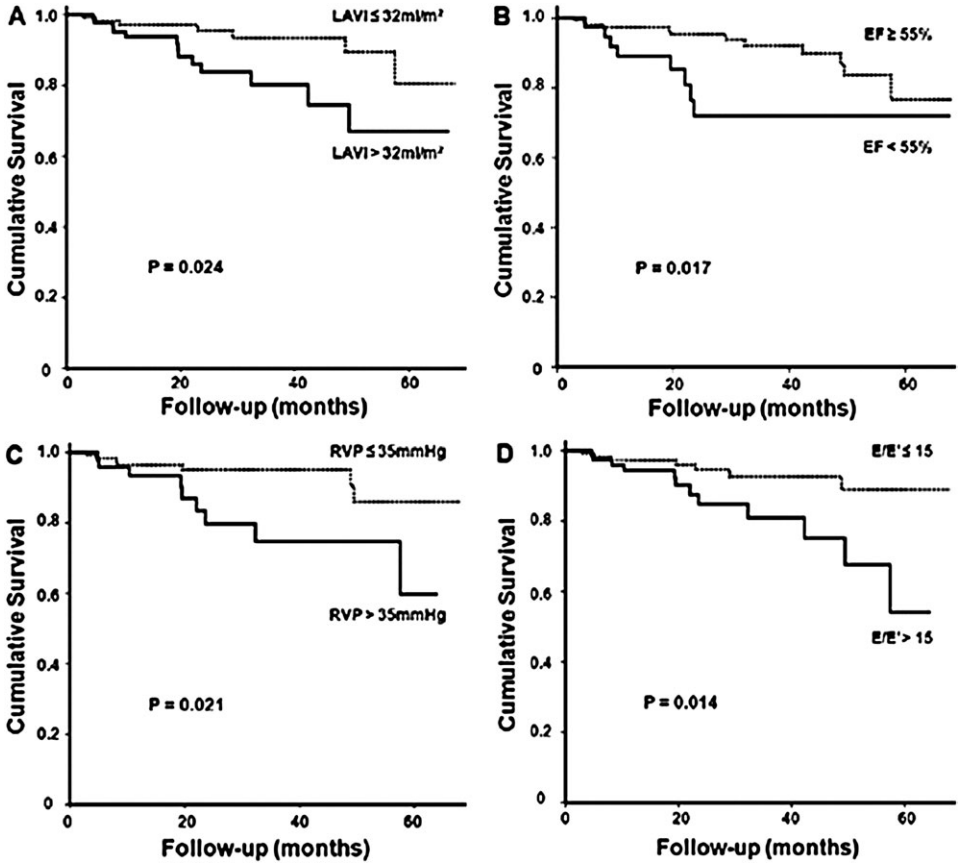

Fig. 2. Kaplan–Meier survival curves for all-cause mortality according to (**A**) LAVI, (**B**) EF, (**C**) RVP and (**D**) the early mitral inflow velocity to peak mitral annulus velocity (E/E′) ratio.

Table 3. Multiple Cox regression models of LAVI for all-cause mortality[a]

Covariates	HR (95% CI)	P-value
EF	1.03 (0.97–1.10)	0.34
LVMI	1.01 (0.99–1.02)	0.64
LAVI	1.05 (1.01–1.10)	0.03
RVP	1.06 (1.00–1.13)	0.035
E/E′	0.97 (0.89–1.05)	0.44
Coronary artery disease	12.30 (2.11–71.90)	0.005
Diabetes	0.82 (0.20–3.61)	0.82
CRP	1.59 (1.20–2.12)	0.002
Albumin	0.68 (0.19–2.42)	0.57
Hemoglobin	1.15 (0.71–1.86)	0.57

[a]Data are reported as HR and 95% CI. E/E′, ratio of early mitral inflow velocity to peak mitral annulus velocity.

Table 4. Multiple Cox regression models of LAVI for cardiovascular mortality[a]

Covariates	HR (95% CI)	P-value
EF	0.99 (0.93–1.05)	0.67
LVMI	1.00 (0.97–1.02)	0.78
LAVI	1.08 (1.02–1.14)	0.006
RVP	1.10 (1.03–1.18)	0.008
E/E′	0.95 (0.86–1.04)	0.28
Diabetes	0.89 (0.14–5.61)	0.89
CRP	1.52 (1.00–2.30)	0.05
Albumin	0.32 (0.07–1.62)	0.17
Hemoglobin	1.16 (0.69–1.96)	0.58

[a]Data are reported as HR and 95% CI. LAVI; E/E′, ratio of early mitral inflow velocity to peak mitral annulus velocity.

hypertrophy and LV systolic dysfunction. LA dilation induces stasis and the development of atrial fibrillation, which predisposes the patient to thromboembolism [17]. Atrial stretch facilitates neurohormonal activation and the secretion of atrial natriuretic peptide, which may have a role in the development of atrial dysrhythmias. The loss of organized atrial activity can also directly precipitate congestive heart failure (CHF) [18]. The LA is not only a passive passage for blood to the LV, but it also affects LV filling because of its contractile function. The LA contributes up to 30% of the total LV stroke volume in normal individuals; this atrial contribution is of particular importance in the context of LV dysfunction to maintain adequate LV stroke volume [3].

Many previous studies have shown that an enlarged LA is predictive of adverse outcomes in patients with cardiovascular conditions such as known cardiomyopathy [19], acute myocardial infarction [20] or pre-existing atrial fibrillation [17]. However, few studies that evaluate the relationship between LAVI and cardiovascular outcomes in ESRD patients have been conducted. Ozdogan *et al.* evaluated the predictive value of increased LA volume in ESRD patients, but their study population mostly consisted of hemodialysis patients [21, 22]. In addition, LV systolic and diastolic functions were not included in the multivariable Cox regression

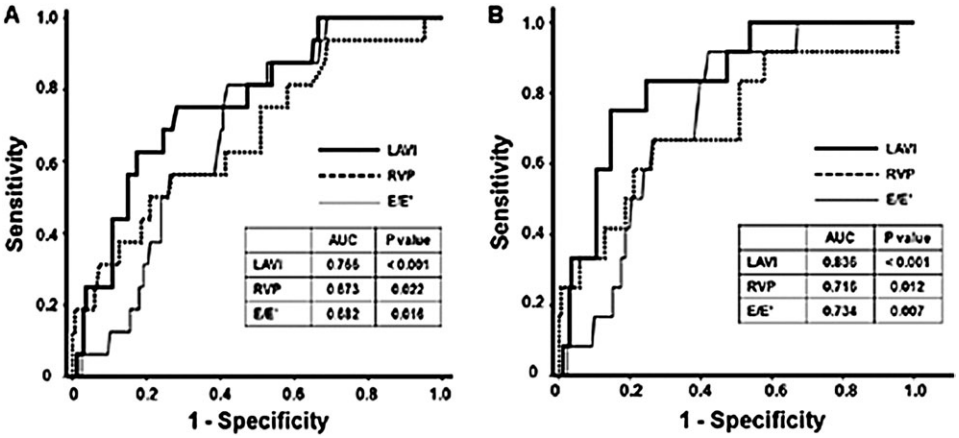

Fig. 3. ROC curve analyses for (**A**) all-cause mortality and (**B**) cardiovascular mortality with calculated AUCs. E/E′, ratio of early mitral inflow velocity to peak mitral annulus velocity.

analysis. Therefore, it was uncertain whether LAVI could predict adverse outcomes independently of other echocardiographic parameters. Our study clearly showed that increased LAVI independently predicted all-cause and cardiovascular mortality in patients with CAPD and provided the highest predictive value among these parameters.

Our findings may have therapeutic implications for patients undergoing CAPD. It has been reported that extracellular volume was greater in CAPD patients and that left ventricular hypertrophy (LVH) was more severe and common in those patients than in hemodialysis (HD) patients [5]. In addition, previous studies showed that such a volume overload was a significant predictor of both all-cause and cardiovascular mortality in ESRD patients [23, 24]. A number of studies have suggested the importance of fluid management in ESRD patients. Particularly, in the European Automated Peritoneal Dialysis Outcome Study, peritoneal ultrafiltration volume >750 mL/day was significantly associated with higher survival in anuric patients [25], suggesting the importance of volume control in these patients. In the present study, we can surmise that patients with enlarged LA were volume expanded, which might explain the higher mortality rate in these patients. Therefore, more attention should be paid to better control of fluid overload in patients with enlarged LA.

In previous studies, LVH has been shown to be an important prognostic factor for cardiovascular events in ESRD patients [2]. An increase in LV mass and cardiac fibrosis has profound consequences in patients with CKD. Sudden cardiac death, linked to abnormal electrical conduction in the distorted and fibrotic ventricle, is a prominent mortal event in ESRD patients. The late stage of LVH and cardiac fibrosis leads to both diastolic and systolic dysfunction and ultimately to clinically recognizable CHF, which has a definite adverse effect on long-term survival in CKD [26]. In contrast, LVH did not predict adverse outcomes in our study patients. Such discrepant findings can be partly explained by the different study population; previous studies mostly consisted of HD patients. Moreover, in those studies, LAVI was not considered in the analyses. Our findings also suggest that patients with PD are more likely to be volume expanded compared to those with HD and that their cardiovascular risk is more affected by volume status than LVH. In addition to LVH, Wang *et al.* [27] reported that E/E′ ratio measured by Doppler echocardiography provided an independent prognostic value for long-term mortality and CV death in CAPD patients. Multiple Doppler echocardiographic variables have been used to assess LV diastolic function. However, these variables reflect the beat-to-beat interaction of LV filling pressure and ventricular compliance, making them sensitive to rapid alterations in ventricular preload and afterload [28]. On the other hand, it is reported that LA size is a more stable indicator to reflect the duration and severity of diastolic dysfunction than any other echocardiographic parameter although it is largely determined by the same factors that influence diastolic LV filling [29]. In addition, Moller *et al.* [20] showed that LAVI was superior to conventional Doppler indices of diastolic function for predicting mortality in patients with acute myocardial infarction. In line with these findings, we demonstrated that increased LAVI was an independent risk factor for all-cause and CV mortality, whereas elevated E/E′ ratio was not, suggesting that LAVI is a more reliable predictor in patients with PD.

There has been much controversy on whether patients with high transport have worse prognosis compared to those with low transport types. Some authors reported that a high transport status was associated with a poor outcome [30], while others failed to demonstrate such finding [31]. However, functional and structural cardiac functions can be influenced by transport status because high transport status has been suggested as a common cause of ultrafiltration failure [32]. On the contrary, in the present study, LAVI, LV systolic function and LVMI were not different between patients with H/HA transporters and those with L/LA transporters. Furthermore, multivariate analysis adjusted for transport status showed that an increased LAVI remained as an independent predictor of all-cause and cardiovascular mortality, whereas H/HA transport status was not. Interestingly, inherent high peritoneal transport may differ from acquired high transport that is generally attributed to the composition of PD solutions and infectious complications, as suggested by Reyes *et al.* [33]. In their study, such inherent high peritoneal transport was not associated with patient survival. Those findings may partly explain the lack of relationship between the peritoneal membrane permeability and mortality in our study.

Our study has several limitations. First, there was an inherent limitation in the observational study design. Second, we could not assess other indicators of extracellular volume such as NT-proBNP measured by immunoassay or extracellular fluid volume/total body water ratio measured by multifrequency electric bioimpedance. However, these assessment tools have not yet been validated in ESRD patients, although some studies showed that elevated NT-proBNP or fluid overload assessed by bioimpedence analysis was predictive of adverse outcomes in this population [23]. Third, baseline RRF was not considered in the multivariate analyses because it was not measured within 2 months after the initiation of PD in 42 patients (19.4%) due to inadequate urine collection and non-compliance. In these patients, RRF was measured between 3 and 12 months. Owing to this inconsistent time of measurement, their data for RRF could not be included in the analyses. Fourth, echocardiographic parameters might act as confounding factors to other parameters because most of those parameters were correlated with each other. Nevertheless, LAVI was the strongest predictor for all-cause and CV mortality in a multivariable Cox model, even after adjustment of such parameters and ROC curve analyses. Finally, echocardiographic examinations were performed only at the initiation of PD. Whether such echocardiographic findings would remain unaltered during the follow-up period is unknown. Serial follow-up of echocardiography may be of help in understanding the natural history of LA remodeling in ESRD. Whether regression of LA size translates into improved CV outcomes requires further studies.

In conclusion, this is the first study, to our knowledge, showing that increased LAVI predicts adverse outcomes better than other echocardiographic, clinical or biochemical parameters in patients with CAPD. Our findings suggest that measurement of LAVI may be of help in risk stratification and in providing therapeutic direction for the management of CAPD patients.

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Conflict of interest statement. None declared.

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Variability of effluent cancer antigen 125 and interleukin-6 determination in peritoneal dialysis patients

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Abstract

Background. Cancer antigen (CA) 125 is a glycoprotein that provides data on the state of the peritoneal membrane in peritoneal dialysis (PD). Interleukin-6 (IL-6) acts as a mediator in acute-phase responses. The study evaluated the usefulness of CA125 and IL-6 in random effluent samples, by assessing their variability in individual patients during clinical practice at the outpatient department.

Methods. This longitudinal prospective study was conducted from 2007 till 2009. Participants included 52 stable PD patients aged $\geq$18 years. Effluent samples were obtained during regular outpatient visits and appearance rates (ARs) were calculated. Inter- and intra-individual variability was determined by the coefficient of variation (CV). A linear mixed model was used to analyse time courses. Furthermore, release patterns of these effluent markers were studied.

Results. CA125-AR of short-term patients ($\leq$24 months) ranged from 39.2 to 766.7 U/min and IL-6-AR from 15.5 to 220.0 pg/min. Long-term patients ($\geq$25 months) had a CA125-AR of 7.3–1534.0 U/min and IL-6-AR of 6.9–956.4 pg/min. Overall, CV_{intra} was 15% in effluent CA125-AR and 28% in IL-6-AR. Intermediate sampling during a 4-h dwell showed a linear increase of CA125 and IL-6 effluent concentrations. The trend of CA125-AR was different ($P = 0.001$) between short- and long-term patients. A negative relationship was found between CA125 ($r = -0.44$, $P = 0.02$) and PD duration.

Conclusions. The clinical relevance of effluent CA125 determinations from an unstandardized dwell during every outpatient visit is reasonable, as judged from the CV_{intra}. The inferior CV_{intra} values of ARs as compared to effluent values indicate that ARs should only be calculated under standardized conditions. A single IL-6 measurement, as a predictor of outcome, should be interpreted cautiously.

Keywords: biomarkers; cancer antigen 125; interleukin-6; mesothelial cells; peritoneal dialysis

Introduction

Cancer antigen (CA) 125 is a high molecular weight (220 kDa) glycoprotein that is constitutively produced by peritoneal mesothelial cells *in vitro* [1]. The number of mesothelial cells in peritoneal effluent of stable peritoneal dialysis (PD) patients is proportional to peritoneal dialysate CA125 concentration [2]. Therefore, it can be regarded as a marker for the mesothelial cell mass in stable PD patients and thus provides data on the state of the peritoneal membrane *in vivo* [3]. Extremely low CA125 concentrations have been found in effluent of patients preceding the diagnosis of peritoneal sclerosis [4]. This is supportive to the contention that a loss of mesothelial cells is implicated in the pathogenesis of peritoneal sclerosis, a serious complication of long-term PD [5]. The small day-to-day