

ORIGINAL ARTICLE

Hemodynamic and pathophysiological characteristics of intradialytic blood pressure elevation in patients with end-stage renal disease

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An increase in systolic blood pressure (SBP) after hemodialysis (intradialytic-HTN) is associated with adverse outcomes in patients on regular hemodialysis. However, the hemodynamic and Doppler echocardiographic characteristics of intradialytic-HTN and its impact on clinical outcomes are unclear. A retrospective analysis of 84 patients (45 men, 70 ± 9 years) stratified into three groups on the basis of SBP response from pre- to post-hemodialysis: G_{HTN} (intradialytic-HTN, SBP increase ≥ 10 mm Hg), $G_{DROP < 15}$ mm Hg (SBP drop < 15 mm Hg), and $G_{DROP \geq 15}$ mm Hg (SBP drop ≥ 15 mm Hg). Hemodynamic and echocardiographic assessments were performed pre- and post-hemodialysis, and patients were followed for 41 ± 17 months. G_{HTN} had higher blood glucose and lower baseline SBP, serum potassium and total cholesterol. Cardiothoracic ratio was smaller, and peak early diastolic mitral annular velocity (E') was lower in G_{HTN} . During hemodialysis, SBP and diastolic blood pressure increased only in G_{HTN} . After hemodialysis, left ventricular (LV) filling pressure (E/E' ratio) decreased only in $G_{DROP \geq 15}$ mm Hg, resulting in a higher E/E' ratio in G_{HTN} than $G_{DROP \geq 15}$ mm Hg. Multivariate logistic regression analysis revealed a positive correlation between blood glucose and intradialytic-HTN, whereas cardiothoracic ratio, pre-hemodialysis SBP and the change in E/E' ratio with hemodialysis were negatively related to intradialytic-HTN. During follow-up, G_{HTN} had more cardiovascular deaths than $G_{DROP \geq 15}$ mm Hg ($P = 0.03$). Multivariate Cox regression analysis showed that lower serum potassium and previous coronary artery disease, but not intradialytic-HTN, were associated with cardiovascular deaths. A higher LV afterload and elevated filling pressures after hemodialysis, indicative of increased cardiovascular stiffening and impaired diastolic filling, may contribute in part to an increased cardiovascular burden in patients with intradialytic-HTN.

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INTRODUCTION

Hypertension promotes cardiovascular stiffening,^{1,2} which impairs left ventricular (LV) diastolic function,³ and contributes to an overall increased risk for cardiovascular comorbidities such as heart failure, myocardial infarction and stroke.⁴ Hypertension is an extremely common ($\sim 90\%$) syndrome in patients with end-stage renal disease on hemodialysis,⁵ and contributes to a higher risk of cardiovascular morbidity and mortality in these patients.^{6,7}

During hemodialysis, excess fluid is removed by ultrafiltration, usually resulting in a reduction in blood pressure (BP). However, in some patients systolic BP (SBP) actually increases pre- to post-dialysis (intradialytic-HTN) despite a reduction in LV preload and body mass by fluid removal.^{8,9} Although it has been reported that intradialytic-HTN is associated with an increased risk of mortality,^{10–12} the pathophysiological mechanisms contributing to intradialytic-HTN are complex and not well understood. Cardiovascular stiffening

increases arterial BP, elevates LV filling pressure and afterload, and impairs LV diastolic function. Therefore, it is possible that profound cardiovascular stiffening and impaired LV diastolic function may contribute in part to an increased cardiovascular burden in patients with intradialytic-HTN. However, to date, no studies have evaluated hemodynamics and LV diastolic function in dialysis patients with and without intradialytic-HTN to support this contention. Such information is valuable as it may enable a better understanding of pathophysiological hallmarks of intradialytic-HTN and allow for the design of more optimal therapeutic options to forestall cardiovascular risk in these patients.

Therefore, the objectives of this study were twofold. First, we aimed to assess hemodynamics and LV diastolic function before and after hemodialysis, to elucidate the pathophysiological characteristics of intradialytic-HTN. Second, we aimed to determine whether intradialytic-HTN is associated with increased cardiovascular and

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noncardiovascular mortality in patients on regular hemodialysis. We hypothesized that advanced cardiovascular stiffening and impaired LV diastolic function contribute to the pathophysiology of intradialytic-HTN.

METHODS

Patient population

Eighty-four patients (45 men, age range 21–77 years) with end-stage renal disease, who had undergone regular hemodialysis in Mie University Hospital and Takeuchi Hospital, were enrolled in the present study between July and August 2008. Patients were excluded if they had atrial flutter/fibrillation, recent myocardial infarction, prior coronary artery bypass graft, LV ejection fraction <50% by two-dimensional echocardiography, severe valvular heart disease, signs of infection, malignancy or previous habitual exercise defined as ≥ 30 min, three times per week. Patients were stratified into three groups according to the changes in supine SBP during hemodialysis; G_{HTN} (SBP increase ≥ 10 mm Hg), $G_{DROP < 15 \text{ mm Hg}}$ (SBP drop < 15 mm Hg) and $G_{DROP \geq 15 \text{ mm Hg}}$ (SBP drop ≥ 15 mm Hg). Two patients whose SBP increased < 10 mm Hg during hemodialysis were excluded as our focus was to elucidate echocardiographic and hemodynamic characteristics in those with a significant increase in their SBP during hemodialysis. One patient was also excluded from the G_{HTN} group as they took etilefrine hydrochloride to elevate his SBP during hemodialysis. Written informed consent was obtained from all patients, and the protocol was approved by the Human Studies Subcommittee of Mie University Graduate School of Medicine.

Hemodialytic procedure

All patients underwent hemodialysis three times per week using either polysulfone ($n = 63$), polyester polymer alloy ($n = 17$), polymethyl methacrylate ($n = 3$) or cellulose triacetate ($n = 1$) dialyzers. Hemodialysis was performed for 3.5–5 h (average 3.8 ± 0.6 h) with acetate bicarbonate-buffered dialysate (sodium 138 – 143 mmol l⁻¹, potassium 2.0 – 2.1 mmol l⁻¹ and bicarbonate 24.0 – 29.4 mmol l⁻¹). During each hemodialysis session, excess fluid was removed to achieve the patient's clinically determined dry weight, and the mean ultrafiltration volume was 1.8 ± 0.8 l. The median (interquartile range) vintage on hemodialysis was 54 (22–102) months.

Study protocol

All medications were continued during all testing sessions. After at least 20 min of supine rest, heart rate, SBP and diastolic BP were measured using an automated BP measuring device to establish pre-dialysis BPs and heart rate. BPs and heart rate were monitored hourly throughout hemodialysis and post-dialysis measurements were performed in the supine position 15 min after disconnecting from the dialysis circuit.

Echocardiography

Two-dimensional Doppler echocardiography (HD11 XE; Philips Medical Systems, Bothell, WA, USA) was performed in the supine or slight left lateral decubitus position before hemodialysis and repeated at the end of hemodialysis by the same sonographer. LV posterior wall thickness at end-diastole, and LV end-diastolic and end-systolic dimensions were measured from the parasternal long-axis acoustic window.¹³

Peak early (E) and late (A) transmitral filling velocities were recorded, and the ratio of E/A was used to assess global LV diastolic filling. Peak early (E') and late (A') diastolic mitral annular velocities were measured at the septal side of the mitral annulus.¹⁴ E' was used to evaluate LV early diastolic filling including LV relaxation,¹⁴ and the ratio of peak early mitral inflow-to-peak early annular velocity (E/E' ratio) was used to estimate LV end-diastolic pressure.^{15,16} All echocardiographic values represent the average of three cardiac cycles.

Clinical outcomes

After baseline measurements of hemodynamics and LV diastolic function, all patients were followed up for 4.5 years (range 7–54 months, average 41 ± 17 months). The study end-point was cardiovascular death or noncardiovascular

death. The causes of death were determined by the attending doctors who were blinded to group assignment.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (Chicago, IL, USA). Data are expressed as mean \pm s.d. in tables and mean \pm s.e. in figures. Continuous data were compared by a one-way analysis of variance (ANOVA) with *post-hoc* analysis or nonparametric Kruskal–Wallis test depending on the outcome of tests for normality. Categorical data were assessed by chi-square test. A two-way repeated measures ANOVA was used to evaluate main (time; group) and interaction effects (time \times group) on hemodynamic and echocardiographic variables before and after hemodialysis. *Post-hoc* analysis was used for pre–post comparisons where either the main or interaction effect was statistically significant. Simple and multivariate binary logistic analyses with forward stepwise procedure ($P < 0.10$ for entry) were applied to assess the relationships between intradialytic-HTN and clinical variables. Event-free survival curves for cardiovascular or noncardiovascular deaths were constructed using Kaplan–Meier method in the three groups, and statistical differences among the three groups were assessed by the log-rank test. The impact of clinical predictors on cardiovascular events was assessed by simple and multivariate Cox regression analyses adjusted for age, gender, hemodialysis vintage and the presence of diabetes mellitus. A P -value < 0.05 was considered significant.

RESULTS

Patient characteristics

As shown in Table 1, G_{HTN} had a higher male/female ratio compared with $G_{DROP < 15 \text{ mm Hg}}$ and $G_{DROP \geq 15 \text{ mm Hg}}$ ($P < 0.05$). Age, height, weight, pre-hemodialysis heart rate and medications were not significantly different among the three subsets of patients. Pre-hemodialysis SBP was significantly lower in G_{HTN} (138 ± 22 mm Hg) than in $G_{DROP < 15 \text{ mm Hg}}$ (154 ± 20 mm Hg) and $G_{DROP \geq 15 \text{ mm Hg}}$ (165 ± 17 mm Hg; $P \leq 0.01$). Likewise, pre-hemodialysis diastolic BP was also lower in G_{HTN} (75 ± 11 mm Hg) compared with $G_{DROP \geq 15 \text{ mm Hg}}$ (85 ± 9 mm Hg, $P < 0.05$). Serum potassium was lower, whereas blood glucose was higher in G_{HTN} compared with $G_{DROP \geq 15 \text{ mm Hg}}$ ($P \leq 0.02$). Interdialytic weight gain in G_{HTN} (1.2 ± 0.6 kg) was not different from $G_{DROP < 15 \text{ mm Hg}}$ (1.7 ± 0.8 kg) or $G_{DROP < 15 \text{ mm Hg}}$ (1.7 ± 0.9 kg, $P = 0.07$; Table 2).

Hemodynamics during hemodialysis

As shown in Figure 1a and Table 2, SBP continuously increased throughout hemodialysis in G_{HTN} , whereas it decreased in the other groups (interaction effect $P < 0.01$). The average change in SBP was 29 ± 12 mm Hg in G_{HTN} , -7 ± 4 mm Hg in $G_{DROP < 15 \text{ mm Hg}}$, and -30 ± 10 mm Hg in $G_{DROP \geq 15 \text{ mm Hg}}$. As a result, post-hemodialysis SBP was significantly higher in G_{HTN} ($P < 0.001$). Similar to SBP, diastolic BP increased only in G_{HTN} (interaction effect $P < 0.01$). Heart rate decreased in all groups with hemodialysis (interaction effect $P = 0.49$; Figure 2 and Table 2).

LV size and Doppler measures of diastolic function

Before hemodialysis, E' was lower in G_{HTN} (4.0 ± 1.2 cm s⁻¹) than in $G_{DROP < 15 \text{ mm Hg}}$ (4.4 ± 1.3 cm s⁻¹) or $G_{DROP \geq 15 \text{ mm Hg}}$ (4.9 ± 1.9 cm s⁻¹), however, this effect did not reach conventional levels of statistical significance ($P = 0.11$). No significant pre-hemodialysis differences were observed in other echocardiographic parameters including E/E' ratio, LV end-diastolic dimension, LV end-systolic dimension or LV ejection fraction.

Hemodialysis decreased LV end-systolic dimension in all three groups ($P \leq 0.06$) with no change in LV ejection fraction (Table 3).

Table 1 Patient characteristics

	ALL	G _{HTN}	G _{DROP} <15mmHg	G _{DROP} ≥15mmHg	ANOVA P
Number	84	21	32	31	-
Male gender, n (%)	37 (44)	14 (67)*†	10 (31)	13 (40)	0.03
Age, years	70±9	70±9	71±8	68±2	0.49
Height, cm	155±9	159±7	154±10	155±10	0.14
Body weight, kg	51.7±10.2	51.2±7.0	51.7±12.8	52.0±9.2	0.96
Body surface area, m ²	1.47±0.17	1.50±0.13	1.46±0.20	1.47±0.16	0.97
SBP, mm Hg	154±22	138±22*†	154±20	165±17	<0.01
DBP, mm Hg	81±12	75±11†	80±13	85±9	<0.01
Heart rate, b.p.m.	77±13	76±13	76±10	78±15	0.71
Cardiothoracic ratio, n (%)	52±6	50±4 (45–58)	54±6 (45–77)	52±6 (38–62)	0.10
<i>Laboratory data</i>					
Serum albumin, gdl ⁻¹	3.6±0.4	3.6±0.4	3.6±0.3	3.7±0.4	0.55
Total cholesterol, mgdl ⁻¹	161±40	132±31*†	171±40	170±38	<0.01
Serum calcium, mgdl ⁻¹	8.9±1.0	8.5±0.6	9.2±1.1	9.0±0.9	0.06
Serum phosphate, mgdl ⁻¹	5.4±1.4	4.8±1.2	5.6±1.4	5.7±1.6	0.05
Serum ALT, U l ⁻¹	11±7	13±8	10±7	10±6	0.54
Serum sodium, mEq l ⁻¹	140±3	140±3	140±4	140±3	0.95
Serum potassium, mEq l ⁻¹	4.6±0.7	4.3±0.7†	4.6±0.8	4.8±0.6	0.02
Hemoglobin, g dl ⁻¹	10.3±1.2	9.7±1.0	10.4±1.3	10.5±1.2	0.08
White blood cells, 10 ³ μl ⁻¹	5.5±1.5	4.9±1.5	5.8±1.5	5.6±1.4	0.06
Platelet count, 10 ⁹ l ⁻¹	173±52	139±57*†	190±43	179±49	<0.01
Blood glucose, mgdl ⁻¹	136±52	158±55†	143±52	114±43	0.01
<i>Comorbidities, n (%)</i>					
Hypertension	76 (90)	17 (81)	29 (91)	30 (97)	0.16
Dyslipidemia	19 (23)	1 (5)	10 (31)	8 (26)	0.07
Diabetes mellitus	39 (46)	13 (62)	16 (50)	10 (32)	0.10
Coronary artery disease	10 (12)	5 (24)	2 (6)	3 (10)	0.14
Chronic glomerulonephritis	30 (35)	6 (29)	8 (25)	15 (16)	0.40
<i>Medication, n (%)</i>					
ARB/ACE-inhibitors	52 (62)	15 (71)	18 (56)	19 (61)	0.54
Calcium channel blockers	43 (51)	13 (62)	16 (50)	14 (45)	0.30
Beta-blockers	12 (14)	3 (14)	6 (19)	3 (10)	0.59
Insulin	11 (13)	4 (19)	4 (13)	3 (10)	0.61
Oral antidiabetic drugs	5 (6)	1 (5)	4 (13)	0 (0)	0.11
Antiphosphate drugs	62 (74)	19 (90)	21 (66)	22 (71)	0.12

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alkaline phosphatase; ANOVA, analysis of variance; ARB, angiotensin II receptor antagonists; DBP, diastolic blood pressure; G_{DROP}<15 mmHg, patients with their SBP drop <15 mmHg after hemodialysis; G_{DROP}≥15 mmHg, patients with their SBP drop ≥15 mmHg; G_{HTN}, patients with their SBP increase ≥10 mmHg after hemodialysis; SBP, systolic blood pressure.
Values are mean ± s.d. or n (%). *P<0.05 vs. G_{DROP}<15 mmHg, and †P<0.05 vs. G_{DROP}≥15 mmHg.

The magnitude of E was significantly lower after hemodialysis in G_{DROP}<15 mmHg (74±19 vs. 63±14 cm s⁻¹, P=0.001) and G_{DROP}≥15 mmHg (71±18 vs. 58±14 cm s⁻¹, P<0.001), but remained unchanged in G_{HTN} (70±21 vs. 68±20 cm s⁻¹, P=0.50). E' was lower after hemodialysis (time effect P<0.001), especially in G_{DROP}<15 mmHg. After hemodialysis, E/E' ratio decreased only in G_{DROP}≥15 mmHg. The ratio was larger in G_{HTN} compared with G_{DROP}≥15 mmHg after hemodialysis (20.0±7.0 vs. 13.8±6.2, P=0.02), suggesting a higher LV filling pressure in G_{HTN} compared with G_{DROP}≥15 mmHg.

Kaplan–Meier analysis

During the follow-up period (average: 41±17 months, range 7–54 months), all-cause deaths were observed in 11 out of 21 patients (52%) in G_{HTN}, 15 out of 32 (47%) in G_{DROP}<15 mmHg and 13 out of 31 (42%) in G_{DROP}≥15 mmHg. No difference was observed in the rates of all-cause death among the groups (Figure 3). Cardiovascular deaths

were observed in six patients in G_{HTN} (29%; two sudden deaths, two brain hemorrhage, one myocardial infarction and one ventricular arrhythmia), four patients in G_{DROP}≥15 mmHg (13%; one myocardial infarction, one aortic dissection, one heart failure and one acute peripheral arterial occlusion) and two patients (7%; one stroke and one brain hemorrhage) in G_{DROP}<15 mmHg. As shown in Figure 4a, G_{HTN} had a higher risk of cardiovascular deaths (29%) than G_{DROP}≥15 mmHg (6%, P=0.03) and G_{DROP}<15 mmHg (13%, P=0.12). Conversely, no difference was observed in the rate of noncardiovascular deaths among the groups (P≥0.53) (Figure 4b). Infection was the leading cause of noncardiovascular deaths in all groups (60% in G_{HTN}, 73% in G_{DROP}<15 mmHg and 45% in G_{DROP}≥15 mmHg).

Correlations between intradialytic-HTN and clinical variables

Results of simple and multivariate logistic regression analyses evaluating clinical predictors of intradialytic-HTN are shown in

Table 2 Hemodynamics during dialysis

	G_{HTN}	$G_{DROP < 15 \text{ mmHg}}$	$G_{DROP \geq 15 \text{ mmHg}}$	ANOVA P
Dialysis vintage, years	5.6 ± 7.3	7.2 ± 8.2	6.8 ± 6.4	0.72
Ultrafiltration volume, kg	1.8 ± 0.8	2.2 ± 0.7	2.1 ± 0.8	0.19
Filtration volume/hour, kg h^{-1}	0.49 ± 0.19	0.58 ± 0.18	0.56 ± 0.19	0.21
Interdialytic weight gain, kg	1.2 ± 0.6	1.7 ± 0.8	1.7 ± 0.9	0.07
Changes in SBP (pre-post), mmHg	-29 ± 12	7 ± 4	29 ± 10	<0.01
Supine SBP, mmHg				
Pre	138 ± 22	154 ± 20	165 ± 17	<0.01
1 h	149 ± 20*	150 ± 20	147 ± 17*	
2 h	157 ± 22*	147 ± 20*	143 ± 17*	
3 h	162 ± 24*†	145 ± 17*	134 ± 15*††	
Post	168 ± 21*††	147 ± 19*	135 ± 14*††	
Supine DBP, mmHg				
Pre	75 ± 11	80 ± 13	85 ± 9	<0.01
1 h	77 ± 8	76 ± 11	78 ± 7*	
2 h	81 ± 5	73 ± 17*	76 ± 9*	
3 h	82 ± 10*	74 ± 8*	74 ± 10*	
Post	82 ± 8*	76 ± 11*	74 ± 10*	
Supine heart rate, b.p.m.				
Pre	76 ± 13	76 ± 11	78 ± 15	0.71
1 h	72 ± 10	72 ± 9*	70 ± 10*	
2 h	71 ± 5	71 ± 7*	73 ± 9*	
3 h	71 ± 7	71 ± 9	74 ± 8*	
Post	72 ± 7	72 ± 8	74 ± 8*	

Abbreviations: ANOVA, analysis of variance; DBP, diastolic blood pressure; $G_{DROP < 15 \text{ mmHg}}$, patients with their SBP drop < 15 mmHg after hemodialysis; $G_{DROP \geq 15 \text{ mmHg}}$, patients with their SBP drop $\geq 15 \text{ mmHg}$; G_{HTN} , patients with their SBP increase $\geq 10 \text{ mmHg}$ after hemodialysis; SBP, systolic blood pressure. Data are expressed as mean ± s.d. or n (%). * $P < 0.05$ vs. pre-dialysis, † $P < 0.05$ vs. 1 h into dialysis, and †† $P < 0.05$ vs. 2 h into dialysis in each group.

Table 4. Multivariate regression analysis showed that blood glucose was positively correlated to intradialytic-HTN (odds ratio: 1.03, 95% confidence interval (CI): 1.00–1.07), whereas cardiothoracic ratio (odds ratio: 0.67, 95% CI: 0.51–0.89), SBP before hemodialysis (odds ratio: 0.87, 95% CI: 0.79–0.95), the change in E/E' ratio during hemodialysis (odds ratio: 0.74, 95% CI: 0.59–0.92), and platelet count (odds ratio: 0.48, 95% CI: 0.29–0.80) were negatively correlated to intradialytic-HTN. Serum phosphate and E' before hemodialysis were negatively correlated to intradialytic-HTN, but neither of these effects reached conventional levels of statistical significance ($P = 0.08$ and $P = 0.07$, respectively).

Predictors of cardiovascular deaths

Results of simple and multivariate Cox proportional hazards model related to cardiovascular deaths are shown in Table 5. Previous coronary arterial disease and lower serum potassium were independently correlated to cardiovascular mortality; however, the relationship between intradialytic-HTN and cardiovascular mortality was not statistically significant. Dyslipidemia and diabetes mellitus appeared to be independently associated with cardiovascular deaths ($P = 0.053$ and $P = 0.06$, respectively).

DISCUSSION

In this study, we demonstrate that in patients with end-stage kidney disease intradialytic-HTN is associated with a smaller cardiothoracic ratio, a higher blood glucose level, and an increased LV afterload and filling pressure after hemodialysis. Intradialytic-HTN is also associated with an increased risk for adverse cardiovascular outcomes.

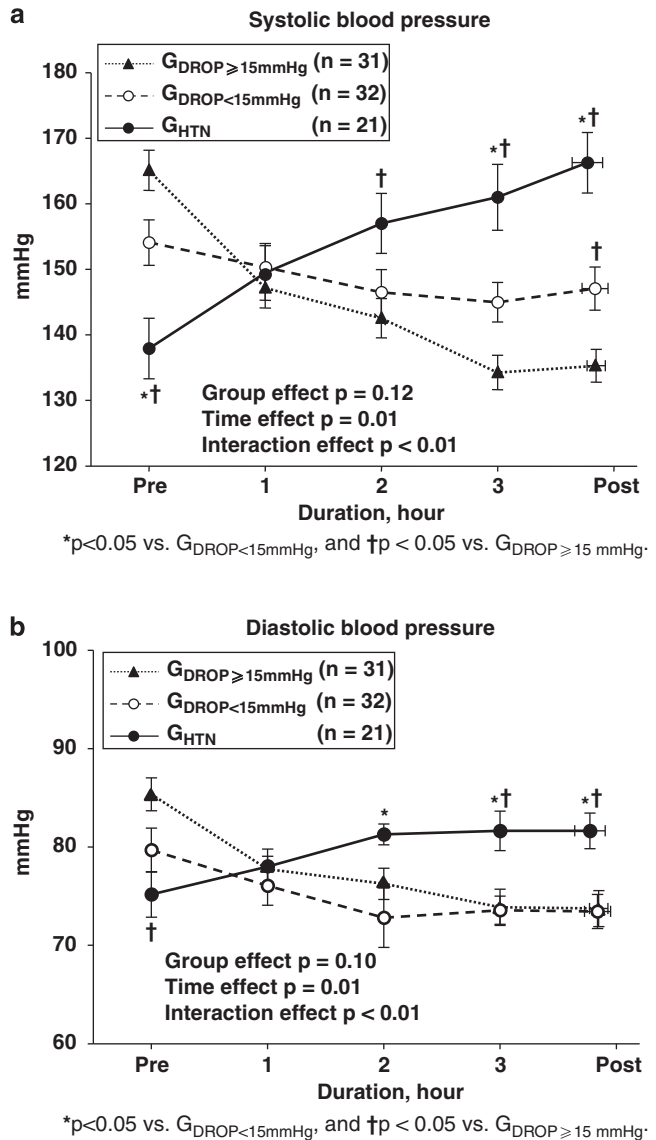


Figure 1 (a) Changes in systolic blood pressure (SBP) during hemodialysis. G_{HTN} indicates patients with their SBP increase $\geq 10 \text{ mmHg}$ after hemodialysis; $G_{DROP < 15 \text{ mmHg}}$, SBP decrease < 15 mmHg after hemodialysis; $G_{DROP \geq 15 \text{ mmHg}}$, SBP decrease $\geq 15 \text{ mmHg}$ after hemodialysis. * $P < 0.05$ vs. $G_{DROP < 15 \text{ mmHg}}$, and † $P < 0.05$ vs. $G_{DROP \geq 15 \text{ mmHg}}$. (b) Changes in diastolic blood pressure during hemodialysis. * $P < 0.05$ vs. $G_{DROP < 15 \text{ mmHg}}$, and † $P < 0.05$ vs. $G_{DROP \geq 15 \text{ mmHg}}$.

These findings suggest that increased cardiovascular stiffening and impaired LV diastolic filling may contribute in part to an increased cardiovascular burden in patients with intradialytic-HTN.

Hemodynamics in intradialytic-HTN during hemodialysis

In the present study, ~20% of patients were categorized as intradialytic-HTN using resting supine SBP, which is a slightly higher percentage than previously reported using upright seated SBP.^{10–12} Orthostatic stress decreases stroke volume and BP, resulting in an increased muscle sympathetic nerve activity. This sympathoexcitation effect to posture change may be particularly profound in the setting of dehydration or fluid loss.¹⁷ Thus, an increase in sympathetic nerve activity may also exist in intradialytic-HTN after hemodialysis in the present study. Our primary objective was to simultaneously evaluate

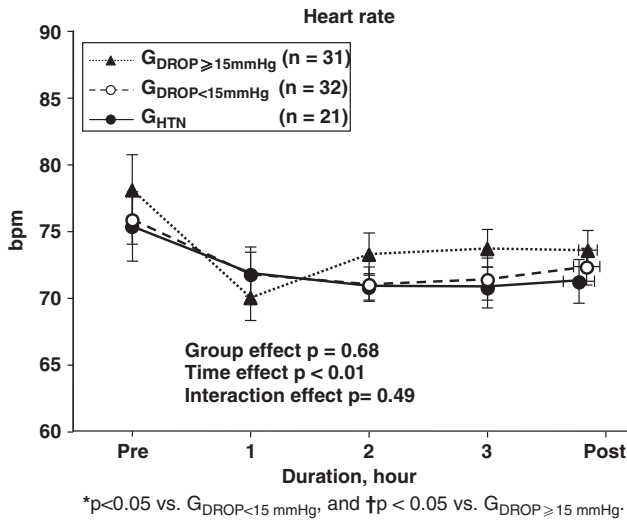


Figure 2 Changes in heart rate during hemodialysis. * $P < 0.05$ vs. $G_{\text{DROP}} < 15 \text{ mmHg}$ and † $P < 0.05$ vs. $G_{\text{DROP}} \geq 15 \text{ mmHg}$.

the impact of ultrafiltration on hemodynamics and echocardiographic parameters in our patients. Thus, to minimize the impact of systemic sympathoexcitation due to postural change, we used supine SBP to define intradialytic-HTN.

Although heart rate decreased during the early stages of hemodialysis in all groups, this reduction was blunted in G_{HTN} . In animals and humans, volume loading increases heart rate¹⁸ presumably due to the Bainbridge reflex mediated through inhibition of vagal outflow or enhanced sympathetic stimulation of the sinoatrial node by stretch receptors in the right and left atria.¹⁸ However, in an animal model of LV diastolic dysfunction and elevated filling pressures, a reduction in venous return ‘unloads’ these stretch receptors, resulting in a reflex-induced decrease in heart rate.¹⁹ Right atrial pressure may be higher in patients with a greater interdialytic weight gain before hemodialysis. Therefore, a larger volume of fluid needs to be removed by ultrafiltration to achieve the patient’s dry weight. We speculate greater interdialytic weight gain in $G_{\text{DROP}} < 15 \text{ mmHg}$ and $G_{\text{DROP}} \geq 15 \text{ mmHg}$ than in G_{HTN} (ANOVA $P = 0.07$) as shown in Table 2 might be related to the larger decrease in heart rate during hemodialysis in these two groups.

Finally, it has been demonstrated that the increase in total systemic vascular resistance is threefold greater during hemodialysis in patients with intradialytic-HTN compared with controls.²⁰ The causes of this exaggerated response in patients with intradialytic-HTN are not completely clear, however, an imbalanced relationship between nitric oxide and endothelium expression is believed to contribute.²⁰ Nevertheless, this elevated systemic vascular resistance in combination with increased cardiovascular stiffness and impaired LV diastolic function would increase cardiovascular burden in patients with intradialytic-HTN, and consequently may contribute to a greater risk of cardiovascular mortality.

Echocardiographic characteristics in intradialytic-HTN

Patients on hemodialysis are characterized by increased cardiovascular stiffening and severely impaired LV diastolic function.⁷ Given the clinical impact of intradialytic-HTN, it is surprising that no previous studies have evaluated LV diastolic function in patients with intradialytic-HTN. Intriguingly, hemodialysis did not affect E, E’ or E/E’ ratio in our G_{HTN} patients. Increased LV afterload prolongs LV

Table 3 Doppler echocardiography

	G_{HTN}	$G_{\text{DROP}} < 15 \text{ mmHg}$	$G_{\text{DROP}} \geq 15 \text{ mmHg}$	Group effect P	Time effect P	Interaction effect P
N	21	32	31			
LVDD, mm						
Pre	43 ± 7	42 ± 6	41 ± 7	0.30	<0.001	0.95
Post	41 ± 9	40 ± 7*	38 ± 7*			
LVDS, mm						
Pre	27 ± 6	27 ± 7	27 ± 6	0.51	0.02	0.62
Post	27 ± 8	25 ± 6*	25 ± 8			
LV ejection fraction, n(%)						
Pre	64 ± 10	65 ± 10	62 ± 11	0.67	0.57	0.93
Post	63 ± 13	65 ± 11	63 ± 14			
E, cm s^{-1}						
Pre	70 ± 21	74 ± 19	71 ± 18	0.41	< 0.001	0.11
Post	68 ± 20	63 ± 14*	58 ± 14*			
A, cm s^{-1}						
pre	92 ± 24	101 ± 21	90 ± 21	0.25	0.002	0.29
post	89 ± 19	89 ± 21*	84 ± 23			
Mitral E/A ratio						
pre	0.81 ± 0.31	0.74 ± 0.15	0.82 ± 0.25	0.49	0.07	0.24
post	0.78 ± 0.24	0.72 ± 0.17	0.71 ± 0.18			
E’, cm s^{-1}						
pre	4.0 ± 1.2	4.4 ± 1.3	4.9 ± 1.9	0.02	0.02	0.64
post	3.6 ± 1.1†	3.9 ± 0.9*	4.7 ± 1.6			
A’, cm s^{-1}						
Pre	7.5 ± 1.2	7.6 ± 1.9	7.2 ± 1.8	0.66	0.89	0.65
Post	7.7 ± 2.8	7.2 ± 1.8	7.1 ± 2.3			
E/E’ ratio						
Pre	18.9 ± 6.9	18.4 ± 7.5	16.5 ± 7.2	0.03	0.13	0.10
Post	20.0 ± 7.0†	16.7 ± 4.4	13.8 ± 6.2*			
LVPWT, mm						
Pre	14 ± 3	14 ± 5	13 ± 3	0.71	0.37	0.70
Post	13 ± 3	13 ± 4	13 ± 3			

Abbreviations: A, peak late mitral inflow velocity; A’, peak late mitral annular velocity; E, peak early mitral inflow velocity; E’, peak early mitral annular velocity; E/E’ ratio, the ratio of peak early mitral filling velocity-to-peak early mitral annular velocity; LVDD, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; LVPWT, left ventricular posterior wall thickness; SBP indicates systolic blood pressure. Values are mean ± s.d. * $P < 0.05$ vs. pre in each group, and † $P < 0.05$ vs. $G_{\text{DROP}} \geq 15 \text{ mmHg}$.

relaxation and may shift LV pressure–volume relationship upward, thereby increasing LV filling pressure.²¹ In the present study, LV filling pressure estimated by E/E’ ratio was unaffected after hemodialysis in G_{HTN} . We speculate that the effect of preload reduction by ultrafiltration on LV filling pressure was counterbalanced by that of increased LV afterload in G_{HTN} , and that elevated LV filling pressure in G_{HTN} after hemodialysis may in part contribute to an increased risk of cardiovascular mortality in G_{HTN} .

Predictors for intradialytic-HTN

The pathogenesis of intradialytic-HTN is proposed to be multifactorial.²² For example, Yang *et al.*¹² reported that intradialytic-HTN was independently associated with volume overload as observed in

patients with a larger cardiothoracic ratio. Volume reduction protocols such as ultrafiltration or lower body negative pressure lower right and left ventricular end-diastolic volume, and decrease external constraint on the LV, especially in patients with volume overload.^{23,24} This decreased constraint on the LV may increase stroke volume and cardiac output²⁵ and eventually elevate BP during hemodialysis. Therefore, in some patients with volume overload, an increase in SBP during the first few hours into hemodialysis was observed, which was followed by a gradual decrease in SBP.²⁶ Contrary to the previous report,¹² cardiothoracic ratio was inversely associated with intradialytic-HTN in the present study. We observed that supine SBP continued to elevate throughout hemodialysis in G_{HTN} . This finding may suggest that volume overload is not always associated with intradialytic-HTN.

We observed that high blood glucose was independently associated with intradialytic-HTN. Exposure to high blood glucose induces endothelial dysfunction²⁷ and LV diastolic dysfunction,²⁸ both of which are predictors of intradialytic-HTN.²² Higher blood glucose in

G_{HTN} might also reflect greater impairments of endothelial function. Exaggerated sympathetic nerve activity has been reported to be another predictor of intradialytic-HTN.^{22,29} Unfortunately, we did not measure catecholamine levels before and after hemodialysis in the present study. However, ultrafiltration would decrease LV stroke volume and induce an overstimulation of sympathetic nerve system in G_{HTN} who may not be severely volume-overloaded. We observed that platelet count was inversely correlated to intradialytic-HTN. This result remains unexplained and may need to be examined in a larger population.

Cardiovascular mortality in patients on hemodialysis

In the present study, serum potassium (odds ratio = 0.31, $P = 0.01$) as well as previous coronary artery disease were independently associated with cardiovascular death. Hyperkalemia and hypokalemia have been reported to be associated with increased mortality in patients on regular hemodialysis.^{30–32} Kovesdy *et al.*³³ reported that a serum potassium level between 4.6 and 5.3 mEq l⁻¹ resulted in the greatest survival, whereas levels <4.0 or ≥ 5.6 mEq l⁻¹ were associated with increased mortality. In the present study, 16 patients out of 84 (19%) had pre-hemodialysis potassium <4.0 mEq l⁻¹, whereas only 7 (8%) had pre-hemodialysis potassium ≥ 5.6 mEq l⁻¹. No patients in G_{HTN} had pre-hemodialysis serum potassium >5.0 mEq l⁻¹. In addition, patients in G_{HTN} appeared to have lower total cholesterol and serum phosphate, and less interdialytic weight gain (ANOVA, $P \leq 0.07$) compared with the other groups. These findings may suggest a possible malnutrition state in intradialytic-HTN.

Recently, Yang *et al.*¹² reported that intradialytic-HTN was associated with high cardiothoracic ratio, and that intradialytic-HTN was an independent predictor for all-cause mortality over a 4-year follow-up period. Contrary to this previous work, we did not find any significant association between intradialytic-HTN and cardiovascular death or all-cause mortality over a similar follow-up period. This discrepancy between studies might be partly explained by differences in patient's characteristics including volume status in the two studies. It is possible that some patients with intradialytic-HTN in the previous study of Yang *et al.*¹² may have had greater LV external constraint caused by volume overload before hemodialysis, and therefore may explain the positive relationship between intradialytic-HTN and cardiovascular death reported by these authors.

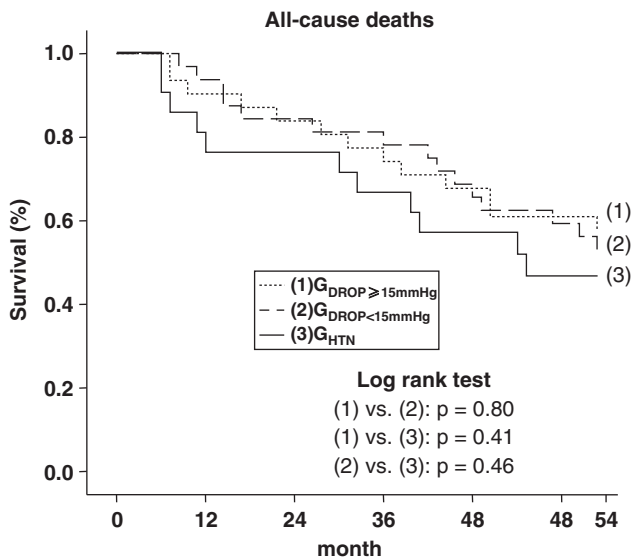


Figure 3 Kaplan–Meier analysis showing all-cause mortality rate in G_{HTN} , $G_{DRO\text{P} < 15 \text{ mmHg}}$, and $G_{DRO\text{P} \geq 15 \text{ mmHg}}$. No difference was observed in all-cause mortality rate among the three groups.

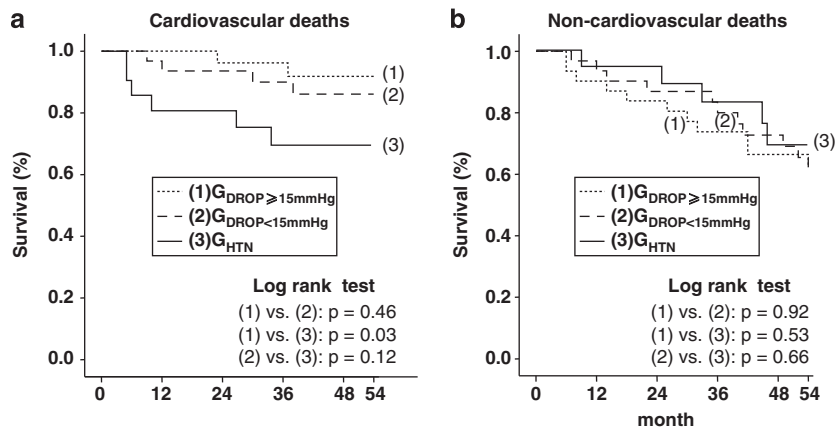


Figure 4 (a) Kaplan–Meier analysis showing cardiovascular mortality rate in G_{HTN} , $G_{DRO\text{P} < 15 \text{ mmHg}}$ and $G_{DRO\text{P} \geq 15 \text{ mmHg}}$. A higher cardiovascular mortality rate was observed in G_{HTN} compared to $G_{DRO\text{P} \geq 15 \text{ mmHg}}$ ($P = 0.03$). (b) Kaplan–Meier analysis showing noncardiovascular mortality rate in G_{HTN} , $G_{DRO\text{P} < 15 \text{ mmHg}}$ and $G_{DRO\text{P} \geq 15 \text{ mmHg}}$. No difference was observed in noncardiovascular mortality rate among the three groups.

Table 4 Logistic regression analysis of the factors for intradialytic-HTN

	Univariate		Multivariate	
	P-value	Odds ratio	P-value	Odds ratio
Age, 10 year	0.72	1.11 (0.63–1.95)		
Male gender	0.01	3.73 (1.31–10.6)	0.95	
Body surface area, m ²	0.43	0.32 (0.18–58.6)		
Dialysis vintage, years	0.43	0.97 (0.90–1.05)		
Filtration volume/hour, kg h ⁻¹	0.09	1.00 (0.99–1.00)	0.34	
Interdialytic weight gain, kg	0.03	0.40 (0.18–0.90)	0.10	
Kt/v	0.27	0.62 (0.25–1.48)		
Cardiothoracic ratio, n (%)	0.06	0.90 (0.81–1.00)	0.005	0.67 (0.51–0.89)
Supine SBP pre, mm Hg	<0.001	0.94 (0.91–0.97)	0.003	0.87 (0.79–0.95)
Supine DBP pre, mm Hg	0.01	0.94 (0.90–0.99)	0.21	
Supine heart rate pre, b.p.m.	0.65	0.99 (0.95–1.03)		
ΔHeart rate (pre-post), b.p.m.	0.92	1.00 (0.96–1.05)		
<i>Echocardiographic variables</i>				
LVDD pre, mm	0.47	1.03 (0.95–1.11)		
LVEF pre, %	0.96	1.12 (0.01–134.6)		
E pre, cm s ⁻¹	0.67	0.99 (0.97–1.02)		
Mitral E/A ratio pre	0.60	1.73 (0.23–13.2)		
E' pre, cm s ⁻¹	0.09	0.72 (0.49–1.06)	0.07	0.37 (0.13–1.07)
E/E' ratio pre	0.43	1.03 (0.96–1.10)		
ΔLVDD (pre-post), mm	0.76	0.99 (0.89–1.09)		
ΔLVEF (pre-post), %	0.96	1.10 (0.02–53.0)		
ΔE (pre-post), cm s ⁻¹	0.048	0.97 (0.95–1.00)	0.94	
ΔE/A ratio (pre-post)	0.63	0.59 (0.07–4.97)		
ΔE' (pre-post), cm s ⁻¹	0.91	1.02 (0.69–1.52)		
ΔE/E' ratio (pre-post)	0.047	0.92 (0.84–0.99)	0.007	0.74 (0.59–0.92)
<i>Laboratory data</i>				
Serum albumin, g dl ⁻¹	0.28	0.49 (0.13–1.81)		
Total cholesterol, mg dl ⁻¹	0.001	0.97 (0.95–0.99)	0.50	
Serum calcium, mg dl ⁻¹	0.03	0.48 (0.25–0.92)	0.10	
Serum phosphate, mg dl ⁻¹	0.02	0.61 (0.40–0.93)	0.08	
Serum ALT, U l ⁻¹	0.29	1.04 (0.97–1.11)		
Serum sodium, mEq l ⁻¹	0.83	1.02 (0.87–1.19)		
Serum potassium, mEq l ⁻¹	0.01	0.35 (0.15–0.80)	0.40	
Hemoglobin, g dl ⁻¹	0.04	0.62 (0.39–0.97)	0.36	
White blood cells, 10 ³ μl ⁻¹	0.02	0.96 (0.92–0.99)	0.37	
Platelet count, 10 ⁹ l ⁻¹	0.002	0.82 (0.73–0.93)	0.004	0.48 (0.29–0.80)
Blood glucose, mg dl ⁻¹	0.03	1.01 (1.001–1.02)	0.03	1.03 (1.003–1.07)
<i>Comorbidities, n (%)</i>				
Diabetes mellitus	0.11	2.31 (0.84–6.37)		
Hypertension	0.10	0.29 (0.07–1.28)		
Dyslipidemia	0.05	0.13 (0.02–1.00)	0.10	
Coronary artery disease	0.06	3.63 (0.93–14.1)	0.40	
<i>Medication, n (%)</i>				
ARB/ACE-inhibitors	0.30	1.76 (0.60–5.13)		
Calcium channel blockers	0.14	2.20 (0.78–6.18)		
Beta-blockers	1.00	1.00 (0.24–4.10)		

Abbreviations: Δ, changes in variables between pre- and post-dialysis; A, peak late mitral inflow velocity; ACE, angiotensin-converting enzyme; ALT, alkaline phosphatase; ARB, angiotensin II receptor antagonists; DBP, diastolic blood pressure; E, peak early mitral inflow velocity; E', peak early mitral annular velocity; Kt/v, dialysis adequacy; LVDD, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Study limitations

There are several limitations to the current study. First, contrary to the previous studies using the upright position to determine intradialytic-HTN,^{10,34} we evaluated echocardiographic parameters

Table 5 Cox regression analysis for cardiovascular mortality in patients with dialysis

	Simple regression		Multiple regression	
	P-value	Odds ratio	P-value	Odds ratio
Age, 10 year	0.73	1.16 (0.51–2.64)		
Male gender	0.32	1.87 (0.55–6.40)		
Body surface area, m ²	0.46	0.15 (0.01–24.3)		
Dialysis vintage, years	0.07	1.09 (0.99–1.20)	0.88	
Intradialytic HTN	0.09	2.79 (0.84–9.11)	0.76	
Filtration volume/hour, kg h ⁻¹	0.89	1.00 (0.99–1.00)		
Interdialytic weight gain, kg	0.87	0.95 (0.50–1.78)		
Kt/v	0.43	1.50 (0.55–4.10)		
Cardiothoracic ratio, %	0.27	1.08 (0.94–1.24)		
Supine SBP pre, mm Hg	0.88	1.00 (0.98–1.03)		
Supine SBP post, mm Hg	0.06	1.02 (0.99–1.05)	0.26	
<i>Echocardiographic variables</i>				
Baseline LVDD pre, mm	0.11	1.08 (0.98–1.20)		
Baseline LVEF, %	0.57	0.17 (0.01–80.1)		
Baseline E wave, cm s ⁻¹	0.74	1.00 (0.97–1.03)		
Baseline mitral E/A ratio	0.65	0.55 (0.04–7.30)		
Baseline E', cm s ⁻¹	0.63	0.87 (0.49–1.54)		
Baseline E/E'	0.96	1.00 (0.92–1.09)		
ΔLVDD (pre-post), cm s ⁻¹	0.89	0.99 (0.88–1.12)		
ΔLVEF (pre-post), %	0.74	2.20 (0.02–215.9)		
ΔE wave (pre-post), cm s ⁻¹	0.27	1.02 (0.98–1.06)		
ΔMitral E/A (pre-post)	0.65	2.04 (0.10–43.5)		
ΔE' (pre-post), cm s ⁻¹	0.33	0.77 (0.46–1.31)		
ΔE/E' (pre-post)	0.12	0.92 (0.83–1.02)		
<i>Laboratory data</i>				
Serum albumin, g dl ⁻¹	0.04	14.9 (1.10–200.3)	0.07	
Total cholesterol, mg dl ⁻¹	0.30	1.01 (0.99–1.03)		
Serum calcium, mg dl ⁻¹	0.17	1.53 (0.83–2.81)		
Serum phosphate, mg dl ⁻¹	0.62	0.88 (0.54–1.45)		
Serum ALT, U l ⁻¹	0.38	1.03 (0.96–1.11)		
Serum sodium, mEq l ⁻¹	0.81	1.02 (0.85–1.24)		
Serum potassium, mEq l ⁻¹	0.04	0.41 (0.18–0.97)	0.01	0.31 (0.12–0.77)
Hemoglobin, g dl ⁻¹	0.82	1.06 (0.65–1.72)		
White blood cells, 10 ³ μl ⁻¹	0.02	0.94 (0.89–0.99)	0.06	
Platelet count, 10 ⁹ l ⁻¹	0.21	0.94 (0.84–1.04)		
Blood glucose, mg dl ⁻¹	0.60	1.00 (0.98–1.01)		
<i>Comorbidities, n (%)</i>				
Diabetes mellitus	0.02	9.97 (1.57–63.4)	0.06	
Hypertension	0.86	0.83 (0.54–6.39)		
Dyslipidemia	0.03	5.62 (1.17–27.1)	0.053	
Coronary artery disease	0.07	3.29 (0.90–12.0)	0.04	4.86 (1.05–22.4)
<i>Medication, n (%)</i>				
ARB/ACE-inhibitors	0.11	7.12 (0.65–78.5)		
Calcium channel blockers	0.32	2.03 (0.50–8.16)		
Beta-blockers	0.89	0.89 (0.18–4.37)		

Abbreviations: Δ, changes in variables between pre and post dialysis; A, peak late mitral inflow velocity; ACE, angiotensin-converting enzyme; ALT, alkaline phosphatase; ARB, angiotensin II receptor antagonists; E wave velocity, early diastolic transmitral velocity; E', peak early velocity of septal mitral annulus; Kt/v, dialysis adequacy; LVDD, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Age, gender, dialysis vintage and the presence of diabetes mellitus were adjusted.

in the supine or slight left lateral decubitus position, and determined intradialytic-HTN by the use of supine SBP. These positions are the standardized postures for assessing LV geometry and function by echocardiography. We believe that the current protocol reduces the

confounding effect of sympathetically mediated changes in hemodynamics in response to postural change. Second, the number of the patients was small for this type of analysis in the present study. In addition, the number of deaths from cardiovascular causes was very small, especially in $G_{\text{DROP}} < 15 \text{ mmHg}$ ($n=2$) and in $G_{\text{DROP}} \geq 15 \text{ mmHg}$ ($n=1$). Owing to the small sample size, our observations need to be examined in a larger sample size and the relationship between intradialytic-HTN and cardiovascular mortality should be evaluated in patients with no excessive volume overload before hemodialysis. Third, the number of the patients with previously diagnosed coronary artery disease was relatively small although patients on regular hemodialysis have a high risk for coronary artery disease.³⁵ Although it is plausible that some of our patients had asymptomatic coronary artery disease,³⁵ our results may not be applicable to a cohort in which the prevalence of coronary artery disease is high. Finally, the usage of a noninvasive measure of LV filling pressure could be considered a limitation of the current study. A couple of previous studies^{15,36} have reported that E/E' ratio provides a reasonable indication of LV filling pressure in patients; however, the precision of this relationship may weaken when evaluated on an individual basis or during significant changes in preload.³⁷ Therefore, some caution is required for the current findings related to LV filling pressure in these patients.

CONCLUSIONS

Intradialytic-HTN was associated with a smaller cardiothoracic ratio and higher blood glucose in patients with end-stage renal disease on regular hemodialysis. Increased LV afterload and elevated LV filling pressure, indicative of increased cardiovascular stiffness and impaired LV diastolic filling, were observed after hemodialysis in patients with intradialytic-HTN, which may contribute at least in part to an increased risk for cardiovascular mortality.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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