Occurrence of Regional Left Ventricular Dysfunction in Patients Undergoing Standard and Biofeedback Dialysis

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• ***Background:*** **Cardiac failure and cardiovascular death are extremely prevalent in dialysis patients. Recurrent subclinical myocardial ischemia is important in the genesis of heart failure in nondialysis patients. We examined whether this phenomenon occurs in response to the stress of hemodialysis (HD).** ***Methods:*** **Eight patients prone to intradialytic hypotension were recruited for a randomized crossover study to compare the development of left ventricular regional wall motion abnormalities during standard (HD) and biofeedback dialysis. Patients underwent serial echocardiography with quantitative analysis to assess ejection fraction and regional left ventricular systolic function during both types of dialysis. Blood pressure and hemodynamic variables also were measured by using continuous pulse wave analysis.** ***Results:*** **Forty-two new regional wall motion abnormalities developed in all 8 patients during HD compared with 23 regional wall motion abnormalities that developed in 7 patients during biofeedback dialysis (odds ratio, 1.8; 95% confidence interval, 1.1 to 3.0). The majority of regional wall motion abnormalities showed improvement in function by 30 minutes postdialysis. Overall mean regional function was significantly more impaired during HD ($P = 0.022$). At peak stress, ejection fraction (measured by percentage of change from baseline) was significantly lower during HD ($P = 0.043$). Blood pressure was higher during biofeedback dialysis, with significantly fewer episodes of hypotension (odds ratio, 2.0; 95% confidence interval, 1.01 to 4.4). Significantly smaller decreases in stroke volume and cardiac output and a greater increment in pulse rate were observed during biofeedback dialysis.** ***Conclusion:*** **This study shows that reversible left ventricular wall motion abnormalities develop during dialysis with ultrafiltration. We also show that this phenomenon can be ameliorated by the improved hemodynamic stability of biofeedback dialysis and therefore is a potential target for intervention.**
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INDEX WORDS: Biofeedback controlled dialysis; cardiac failure; echocardiography; hemodialysis (HD) complications; myocardial stunning; pulse wave analysis.

THE CARDIOVASCULAR mortality rate of dialysis patients is extremely high, at least 30 times greater than that in age-matched controls. Often, this is manifest as cardiac failure, which develops in up to 25% to 50% of hemodialysis (HD) patients and confers a dramatic decrease in probability of survival.[1] In addition to "conventional" cardiovascular risk factors, dialysis patients are subject to unique metabolic and hemodynamic derangements, the so-called "uremic" risk factors. The pathophysiological state of uremic cardiac disease is not fully defined, but may include factors related directly to the HD procedure.

Recurrent subclinical myocardial ischemia (occurring without acute atherosclerotic plaque rupture) is one possible adverse effect of dialysis. Short intermittent HD treatments exert significant hemodynamic effects, and 20% to 30% of treatments are complicated by intradialytic hypotension (IDH).[2,3] One study showed evidence of clinically silent decreases in myocardial perfusion developing during HD,[4] and it is well recognized that cardiac troponin-T levels increase acutely after dialysis, possibly indicating subclinical myocardial cell injury.[5] Furthermore, HD patients are particularly susceptible to myocardial ischemia. In addition to the high prevalence of coronary artery atheroma, dialysis patients with diabetes have had decreased coronary flow reserve, even in the absence of coronary vessel stenoses.[6] Increased arterial stiffness, dysregulation of blood pressure (BP) control caused by abnormal baroreflex sensitivity, and vasoregulatory failure leading to the increased reliance of

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Table 1. Patient Demographics

Patient No.	Age (y)	Months on Dialysis Therapy	Cause of End-Stage Renal Failure	Atherosclerotic Vascular Disease	Diagnosed IHD	LV Mass Index ($g/m^{2.7}$)	Angiogram	Antianginal or BP-Lowering Drugs
1	68	45	APKD	Yes	Yes (angina)	63.8	No*	Diltiazam, 180 mg 1 × d
2	58	40	Obstructive uropathy	No	No	94.2	No	
3	53	15	Crescentic glomerulonephritis	Yes	Yes (angina)	86.9	No	Nifedipine, 60 mg 1 × d
4	72	47	Unknown	Yes	Yes (MI)	79.7	Yes†	ISMN, 30 mg 1 × d
5	69	59	Diabetes	Yes	Yes (3 MIs)	86.5	No	Lisinopril, 40 mg 1 × d
6	73	36	ARVD	Yes	No	94.6	No	Atenolol, 50 mg 1 × d
7	71	13	ARVD	Yes	No	96.4	No	Lisinopril, 20 mg 1 × d
8	80	22	Diabetes	Yes	Yes (angina)	80.8	No	
Mean ± SD or total (%)	8.0 ± 8.6	34 ± 16		7 (88)	5 (63)	85.4 ± 10.7	1 (13)	

Abbreviations: APKD, adult polycystic kidney disease; ARVD, atherosclerotic renovascular disease; MI, myocardial infarction; ISMN, isosorbide mononitrate.

*Patient 1 recently had undergone a dipyridamole stress test showing a fixed apical perfusion defect with reversible inferior wall hypoperfusion.

†Angiogram result for patient 4: circumflex occluded with some retrograde filling, right coronary artery occluded with good retrograde filling, and left anterior descending artery with some atheroma, but no occlusive disease.

BP on cardiac output also increase the risk for myocardial hypoperfusion.[7,8]

As such, the hemodynamic stress of dialysis potentially may cause transient myocardial ischemia that is associated with and followed by left ventricular (LV) dysfunction. The latter is known as myocardial stunning.[9] Repeated episodes of ischemia and stunning may be cumulative and lead to the phenomenon of myocardial hibernation, which, in turn, contributes to chronic heart failure in patients with ischemic heart disease.[10]

Several strategies have been used in an attempt to improve the hemodynamic tolerability of dialysis and decrease IDH. One such technique is biofeedback dialysis (Hemocontrol; Hospal, Lyon, France), which responds to significant decreases in relative blood volume (defined on an individual basis) by temporarily decreasing the ultrafiltration (UF) rate and increasing the dialysate sodium conductivity. This is done within defined limits to ensure that total UF and sodium depuration are unaffected. Biofeedback dialysis has decreased IDH episodes in several studies.[11,12]

Therefore, we performed a study to test the hypothesis that significant reversible abnormalities in regional LV function occur in response to standard HD. We also compared standard HD with biofeedback dialysis to determine whether improving the hemodynamic tolerability of dialysis affected the development of LV regional wall motion abnormalities.

METHODS

Patients

Eight long-term HD patients prone to IDH were recruited. All were men and had been on dialysis therapy for more than 12 months. All had LV hypertrophy (defined as LV mass index $> 51 g/m^{2.7}$) on analysis of baseline echocardiograms, and there was a high prevalence of atherosclerotic vascular disease. Six patients were treated with aspirin; 1 patient, clopidogrel; and 5 patients, statins. Individual patient characteristics are listed in Table 1, and baseline biochemistry values are listed in Table 2.

Study Protocol

On entry to the study, patients had their dry weight confirmed with reference to clinical examination. After this, dry weight and antihypertensive medications were unchanged for the duration of the study. Patients were randomly assigned to group A or B. Group A patients were started on standard thrice-weekly HD, whereas group B

Table 2. Baseline Laboratory Parameters

	Hemoglobin (g/dL)	Kt/V_{urea}	Sodium (mEq/L)	Potassium (mEq/L)	Parathyroid Hormone (pg/mL)	Calcium (mg/dL)	Phosphate (mg/dL)	Calcium × Phosphate Product (mg^2/dL^2)
Mean	10.4	1.0	140.6	4.5	391.9	9.7	4.6	44.8
SD	1.0	0.3	3.7	0.9	262.5	0.5	1.8	18.6

NOTE. Kt/V_{urea} was calculated according to Daugirdas. To convert hemoglobin in g/dL to g/L, multiply by 10; calcium in mg/dL to mmol/L, multiply by 0.2495; phosphate in mg/dL to mmol/L, multiply by 0.3229; parathyroid hormone in pg/mL to ng/L, multiply by 1.

patients started on thrice-weekly biofeedback dialysis treatment. Both groups underwent 1 week of the dialysis therapy before undergoing a monitored session during 1 of the midweek dialysis sessions during the second week, consisting of serial echocardiography and noninvasive hemodynamic monitoring (using a Finometer; Finapres Medical Systems, Arnhem, The Netherlands). At the end of the second week, patients then crossed over to the other dialysis modality, thereby acting as their own controls. After an additional week on the alternate modality, patients underwent a second monitored session.

All patients gave informed consent before the study start, and ethical approval for the project was granted by Derbyshire Local Research Ethics Committee.

Echocardiography

Two-dimensional echocardiography was performed serially throughout dialysis sessions by using commercially available equipment (Sonos 5500; Hewlett Packard, Andover, MA). A single experienced technician (who was blinded to dialysis modality) carried out all measurements with the patients in the left lateral position. Images were recorded before starting dialysis (baseline), at 120 and 240 minutes during dialysis, and 30 minutes after dialysis was finished (recovery). Standard apical 2-chamber and 4-chamber views (to visualize the LV endocardial border in 2 planes at 90° to each other) were recorded onto super-VHS videotape for offline analysis.

Videotaped images were subsequently analyzed by using a personal computer–based digitizing program (Echo-CMS; MEDIS, Leiden, The Netherlands), as previously described.[13] Three consecutive heartbeats were analyzed for each time point (extrasystolic beats were excluded). Endocardial borders (excluding papillary muscles) were traced semiautomatically for each video frame of the 3-beat sequence, and any anomalies were corrected manually. Maximal displacement of the endocardial border from a center point was then measured over each of 100 chords around the LV wall, corrected for end-diastolic LV circumference, and expressed as percentage of shortening fraction (SF). Each apical view was divided into 5 segments, and SF for the chords in each segment was averaged so that 10 regions of the left ventricle were assessed at each time. New regional wall motion abnormalities were defined as segments that showed a decline in SF greater than 20% from baseline. We calculated mean SF for all 10 segments ($SF_{(mean)}$) and for segments that developed new regional wall motion abnormalities ($SF_{(WMA)}$). Peak stress was defined for each patient as the point during the first monitored dialysis session at which most regional wall motion abnormalities were present (either 120 or 240 minutes). When comparing dialysis modalities, the same time point was used in the second dialysis session.

Ejection fraction (EF) was calculated by using LV volumes at end-systole and end-diastole, measured by using the biplane disk method. Left atrial volume, which has been used as a marker of diastolic function in HD patients,[14] was calculated by using single-plane Simpson's method from the apical 4-chamber view and indexed for body surface area. LV mass index was calculated from each patient's original baseline images by using the Devereux formula corrected for height.[2,7]

Finometer

The Finometer allows continuous noninvasive pulse wave analysis at the digital artery. The technology uses the finger-clamp method to record digital artery pulse waveform and from this reconstructs a central aortic waveform that allows calculation of a full range of hemodynamic variables on a continuous basis for each heart beat.[15] These include BP, pulse rate, stroke volume, cardiac output, and peripheral resistance. This technology is being used increasingly to assess long-term dialysis patients.[2,16] Previous work validated the Finometer against invasive hemodynamic measurements in healthy individuals, unstable intensive care patients, and cardiac surgery patients, a proportion of whom had vascular calcification.[17] This showed the Finometer to be accurate in tracking relative change. Data therefore are presented as percentage of change from baseline, except for BP, which is calibrated against brachial readings by using a return-to-flow method, and for this, absolute values are shown. Baroreflex sensitivity also was calculated from the regression slope between continuous interbeat interval and beat-to-beat BP changes. Three consecutive changes in the R-R interval in the same direction were required before a phase shift calculation (incorporated into the Finometer software) was performed. Baroreflex sensitivity measured in this way is a composite marker of the overall activity of the autonomic nervous system.[18]

HD Details

Dialysis was performed using Hospal Integra monitors (Hospal, Lyon, France). Both HD and biofeedback dialysis were performed using low-flux polysulfone dialyzers,

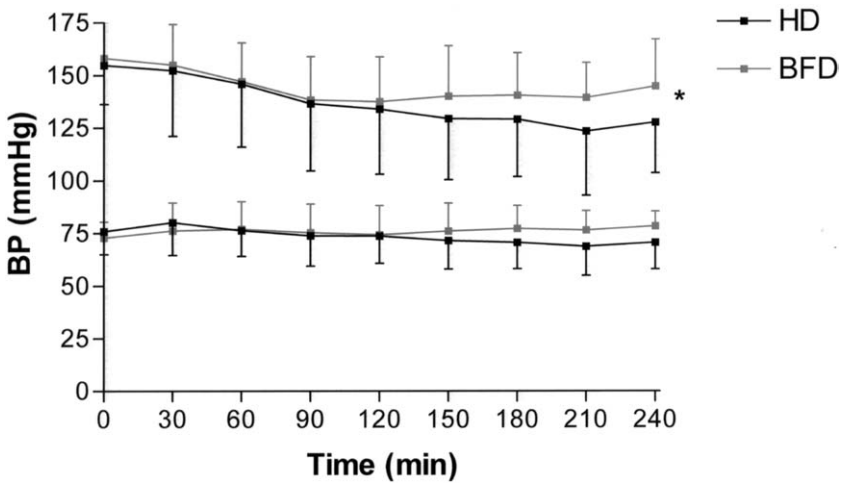


Fig 1. Population BP (systolic and diastolic) data during standard (HD) and biofeedback (BFD) dialysis. *$P < 0.001$ by analysis of variance. For clarity, mean arterial pressure is omitted, but this also was significantly higher during BFD ($P < 0.001$).

either 1.8 or 2.0 m^2, per individual patients' usual prescriptions (LOPS 18/20; Braun Medical Ltd, Sheffield, UK). For both treatments, dialysate contained sodium, 138 mmol/L; potassium, 1 mmol/L; calcium, 1.25 mmol/L; magnesium, 5 mmol/L; bicarbonate, 32 mmol/L; glucose, 1 g/L; and acetate, 3 mmol/L. All treatments were of 4 hours' duration, and anticoagulation was achieved by using unfractionated heparin. Dialysate flow was 500 mL/min, and dialysate temperature was set at 37°C. For each session, net fluid removal was set on an individual basis according to ideal dry weight. Blood pump speed varied between 250 and 450 mL/min, depending on the patient's vascular access, but each individual patient had the same blood flow for their 2 monitored sessions.

For standard HD, dialysate sodium conductivity was set at 13.6 mS/cm. For biofeedback dialysis, conductivity limits were set at 13.0 and 14.0 mS/cm. Automatic adjustment of dialysate conductivity by the dialysis monitor during Hemocontrol (Hospal) has been shown to achieve equivalent overall dialysate conductivity and therefore equal changes in plasma water sodium concentrations.[19] Limits for relative blood volume were set on an individual basis depending on measurements obtained the week before echocardiographic assessment.

Statistical Analysis

Results are expressed as mean ± SD unless otherwise stated. Echocardiographic, BP, and hemodynamic data were analyzed by using 1-way analysis of variance with a design for repeated measures and Bonferroni test to correct for multiple comparisons. Frequencies of IDH and new regional wall motion abnormalities occurring during each dialysis modality were compared by using Poisson regression. For other data, paired *t*-test was used after significant deviations from a normal distribution were excluded with the Kolmogorov-Smirnov test. An α error at P less than 0.05 was judged to be significant.

RESULTS

BP Data

During standard HD, systolic BP was 135 ± 30.8 mm Hg, diastolic BP was 73.2 ± 13.9 mm Hg, and mean arterial pressure was 93.9 ± 19.8 mm Hg. During biofeedback dialysis, all 3 BP parameters were higher; mean systolic BP was 143.1 ± 21.1 mm Hg ($P < 0.001$),

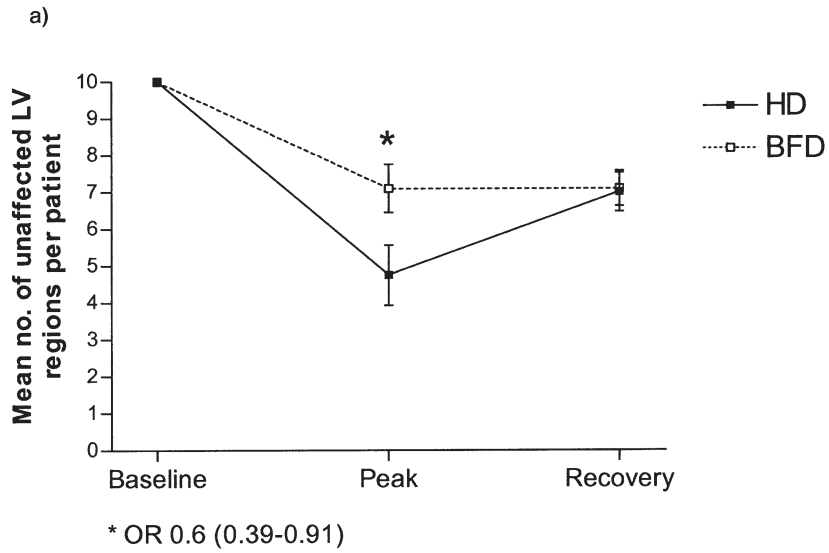
Table 3. UF Volume, Body Mass Index, and UF Volume Indexed to Body Mass Index for Individual Patients During Both Types of Dialysis

Patient No.	Body Mass Index (kg/m^2)	UF Volume HD (l)	Indexed UF Volume HD	UF Volume BFD (l)	Indexed UF Volume BFD
1	22	0.4	1.8	0.5	2.3
2	24	1.3	5.4	2.0	8.2
3	29	2.2	7.6	3.2	11.0
4	21	1.2	5.7	1.8	8.5
5	23	0.5	2.2	0.4	1.8
6	24	2.7	11.1	3.3	14.1
7	27	0.4	1.5	0.4	1.5
8	29	3.6	12.4	3.7	12.6
Mean ± SD	24.9 ± 3.0	1.54 ± 1.19	6.0 ± 4.2	1.91 ± 1.38	7.5 ± 5.1

Abbreviation: BFD, biofeedback dialysis.

mean diastolic DBP was 76.4 ± 12.3 mm Hg ($P > 0.05$), and mean arterial pressure was 100.1 ± 3.3 mm Hg ($P < 0.001$). BP gradually decreased during the second half of HD treatments, whereas BP was maintained during the second half of biofeedback dialysis sessions, therefore accounting for the difference in mean BP values. BP data are shown in Fig 1.

IDH was defined as a systolic BP less than 90 mm Hg or a decrease in systolic BP greater than 40% from baseline in association with the classic symptoms of hypotension (dizziness, cramps, flushing). There were no episodes of symptomatic hypotension during the 16 monitored sessions, but we observed 24 asymptomatic episodes of IDH with HD compared with 12 during biofeedback dialysis (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.01 to 4.4). These findings were in the context of a slightly greater UF volume during biofeedback



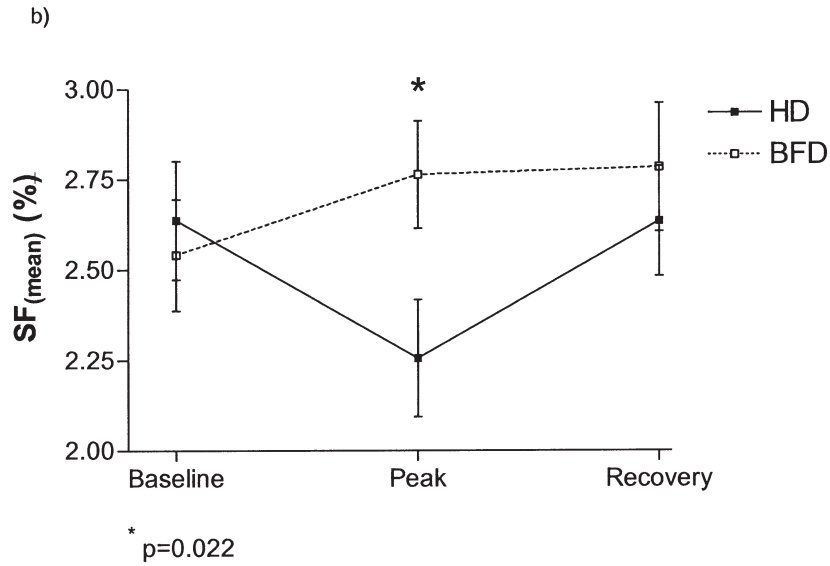


Fig 2. (A) Mean number of unaffected LV regions during standard (HD) and biofeedback dialysis (BFD). Only new regional wall motion abnormalities were counted and therefore all regions are scored as unaffected at baseline. Baseline is before the start of dialysis, peak stress is the point at which most regional wall motion abnormalities were present during dialysis, and recovery is 30 minutes postdialysis. (B) Overall mean regional LV function (SF) during HD and BFD. (A, B) Data expressed as mean ± SE.

dialysis (1.91 ± 1.38 L) compared with HD (1.54 ± 1.19 L), although this difference was not statistically significant. Individual UF volumes and body mass indices are listed in Table 3.

Echocardiographic Data

Throughout the study, all patients were in sinus rhythm and no patient had significant valvular disease or pulmonary hypertension. SF at baseline in all regions was compared on an individual basis for each type of dialysis. There were no significant differences in baseline SF in any patient. This was done to ensure repeatability of images and measurement technique and also to ensure that the regional wall motion abnormalities that persisted at 30 minutes postdialysis were not permanent.

All 8 patients developed regional wall motion abnormalities at peak stress during HD compared with 7 patients during biofeedback dialysis. More regional wall motion abnormalities developed during HD compared with biofeedback dialysis, with a total of 42 regional wall motion abnormalities during HD compared with 23 regional wall motion abnormalities during biofeedback dialysis (OR, 1.8; 95% CI, 1.1 to 3.0). There also was a difference comparing the rate of unaffected regions between dialysis modalities (OR, 0.60; 95% CI, 0.39 to 0.91). By 30 minutes post-HD, 32 affected segments (76%) showed complete or partial resolution, whereas after biofeedback dialysis, 15 regional wall motion abnormalities (65%) improved. However, at 30 minutes post-HD, 24 affected regions (30%) still had SF greater than 20% less than baseline, and after biofeedback dialysis, this figure was similar at 23 (29%; OR, 1.0; 95% CI, 0.59 to 1.83). These data are shown in Fig 2, and 1 representative patient's regional wall motion is shown in Fig 3.

Data for $SF_{(mean)}$, $SF_{(WMA)}$, and EF are shown in Table 4 and Figs 2, 4, and 5. $SF_{(WMA)}$ decreased at peak stress during both types of dialysis and improved in recovery. $SF_{(WMA)}$ decreased by a greater percentage from baseline during HD (−43% ± 15.1%) compared with biofeedback dialysis (−37.8% ± 16.0%), but this difference did not reach statistical significance ($P = 0.19$). In view of this trend toward a more severe decrease in $SF_{(WMA)}$ and also the greater number of regional wall motion abnormalities, $SF_{(mean)}$ decreased to a significantly greater degree at peak stress during HD (−10.3% ± 48.4% from baseline) compared with biofeedback dialysis (+13.5% ± 48.4%; $P = 0.022$). At baseline and recovery, there were no statistically significant differences in either $SF_{(mean)}$ or $SF_{(WMA)}$ between the 2 types of dialysis.

At peak stress, EF was significantly lower during HD compared with biofeedback dialysis ($P = 0.043$), whereas no difference was found during recovery. Table 5 lists the remaining LV and left atrial dimensions before and after HD and biofeedback dialysis. There were no differences in any measurements comparing dialysis modalities.

Hemodynamic Data

Baseline hemodynamic data were compared between the 2 dialysis modalities to ensure that there were no systematic errors; no difference in any variable was observed.

Pulse rate increased for the entire study period by a mean of +5.0% ± 2.5% greater than baseline during biofeedback dialysis, whereas pulse rate changed very little during HD (mean, +0.4% ± 2.4%; $P < 0.01$). Stroke volume decreased during both treatments, but to a significantly lesser extent during biofeedback dialysis. Mean stroke volume for the entire HD session was −26.2% ± 7.2% from baseline compared with a mean of −20.2% ± 7.3% ($P < 0.001$) during biofeedback dialysis. Cardiac output showed a similar pattern, decreasing during both treatments, but less so during biofeedback dialysis. Mean cardiac output was −26.4% ± 7.2% during HD compared with a mean of −18.2% ± 7.8% during biofeedback dialysis ($P < 0.001$). Mean peripheral resistance during HD was +33.4% ± 11.2% greater than baseline, which was statistically greater than the mean of +28.6% ± 12.2% during biofeedback dialysis ($P < 0.05$). Mean baroreflex sensitivity was greater during HD at 7.3 ± 5.6 ms/mm Hg compared with a mean of 5.6 ± 3.4 ms/mm Hg during biofeedback dialysis ($P < 0.001$). Baroreflex sensitivity also showed more variability during HD (coefficient of variability, 76.4%) compared with biofeedback dialysis (coefficient of variability, 60.7%), signifying increased autonomic activation during the former modality. Hemodynamic data are shown in Fig 6.

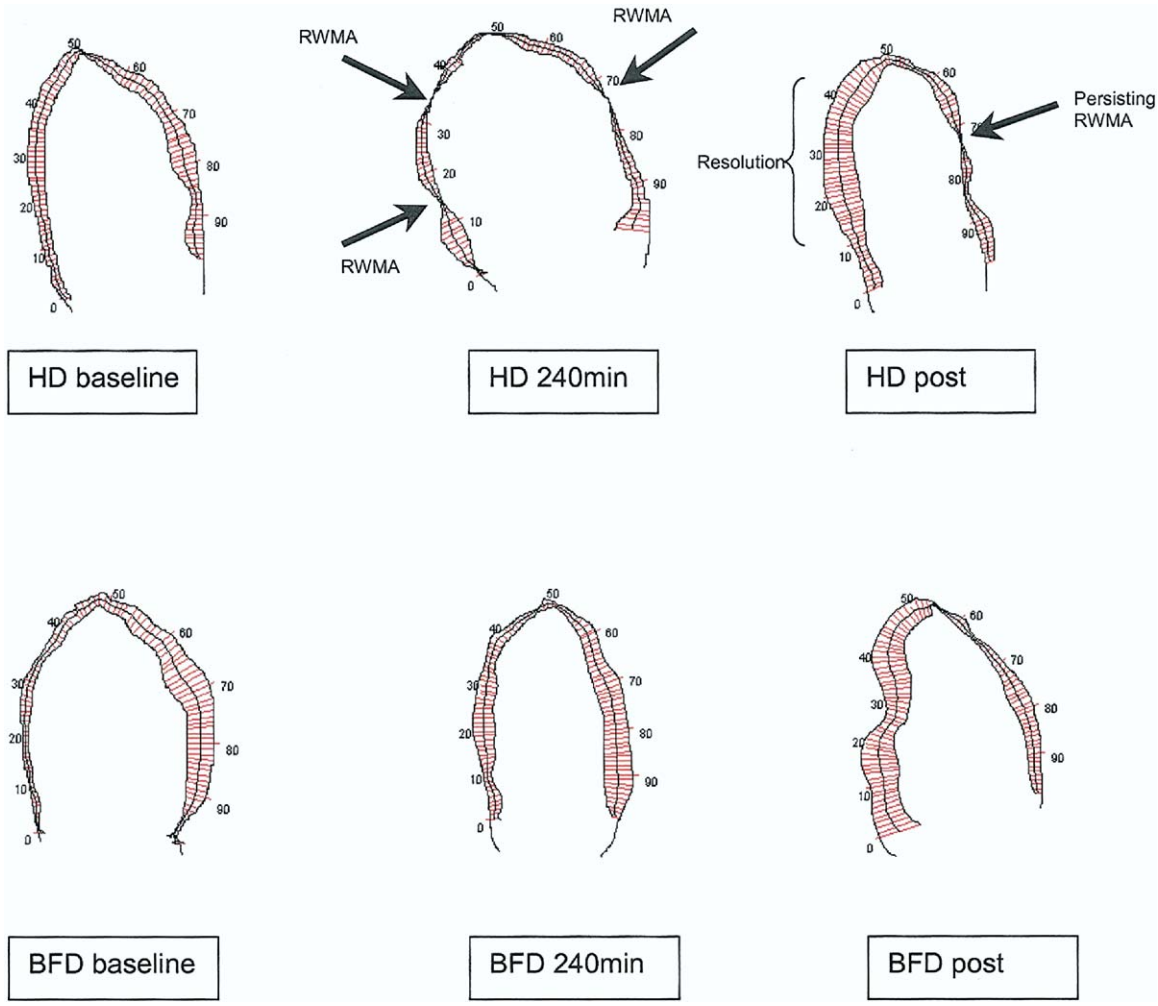


Fig 3. Analysis of LV wall motion (2-chamber view) of 1 representative patient (number 3) during standard (HD) and biofeedback controlled (BFD) dialysis. Wall motion is measured over each of 100 chords around the ventricular wall. Baseline traces are similar. By 240 minutes, 3 new regional wall motion abnormalities (RWMAs; arrows) have developed during HD, but the same regions are unaffected during BFD. At 30 minutes post-HD, 2 of the RWMAs have resolved and 1 persists (arrow).

DISCUSSION

We show that reversible decreases in LV regional wall motion occur during standard HD and, to a significantly lesser extent, during biofeedback dialysis. Although we did not measure blood flow before and after HD, we believe the LV dysfunction that develops during the procedure most likely is caused by myocardial ischemia. Previous studies also suggested that dialysis can induce subclinical myocardial ischemia,[4,20] but this is the first to suggest that this phenomenon can be ameliorated.

The development of new LV regional wall motion abnormalities during physiological or pharmacological stress occurs in response to ischemia, and its onset precedes that of symptoms and electrocardiographic changes. This forms the basis of stress echocardiography.[21] Subclinical ischemia therefore is the likely cause of the LV regional wall motion abnormalities that we show in response to the stress of dialysis. The majority of affected regions showed some degree of improvement by 30 minutes after dialysis, and SF at baseline was similar in each individual comparing the 2 dialysis sessions,

Table 4. Global (EF) and Regional (SF) LV Function During Standard (HD) and Biofeedback Dialysis

	EF (%)	$SF_{(mean)}$ (%)	$SF_{(WMA)}$ (%)
HD			
Baseline	50.1 ± 10.7	2.64 ± 1.5	2.98 ± 1.7
Peak	48.7 ± 12.3	**2.26 ± 1.4***	**1.69 ± 1.0†**
Recovery	53.4 ± 13.3	2.64 ± 1.3	**2.38 ± 1.3†‡**
Biofeedback dialysis			
Baseline	46.1 ± 12.3	2.54 ± 1.4	3.12 ± 1.6
Peak	53.1 ± 12.1	2.76 ± 1.3	**1.90 ± 1.0†**
Recovery	54.4 ± 15.4	2.78 ± 1.6	**2.67 ± 1.7†‡**

NOTE. Baseline is before the start of dialysis, peak stress is the point at which most regional wall motion abnormalities were present during dialysis, and recovery is 30 minutes postdialysis. Results that are of statistical significance are indicated in bold.

*$P < 0.05$.

†$P < 0.001$ versus baseline by analysis of variance.

‡$P < 0.001$ versus peak by analysis of variance.

which indicates that these regions do not sustain irreversible damage during a short time scale. However, approximately a third of regions had a persistent decrease in SF at 30 minutes postdialysis. Stunned myocardium can take up to 24 to 48 hours to recover function after an ischemic insult (which matches the interdialytic interval).[22] Therefore, this would be consistent with the hypothesis that stunning occurred in our patients, with regional wall motion abnormalities persisting despite conditions in which any perfusion abnormalities would be expected to have resolved. However, for conclusive evidence of myocardial stunning, myocardial blood flow and LV function need to be measured simultaneously.

Repeated episodes of stunning have been shown to be cumulative, leading to more prolonged LV dysfunction.[23] This is thought to be an important mechanism in the development of hibernation, which, in turn, contributes to chronic heart failure.[24] If myocardial stunning is induced by HD, as our study suggests, the process of HD itself, repeated 3 times weekly, may contribute to chronic cardiac dysfunction in this patient group. Certainly, patients who receive a kidney transplant have significantly decreased all-cause and cardiovascular death rates,[25] and renal transplantation in patients with established heart failure improves LV EF and symptoms.[26] It is possible that some of this benefit seen after transplantation may be caused by the avoidance of dialysis and its negative effects. In addition, "uremic cardiomyopathy" is characterized histologically by myocardial fibrosis, which is similar to hibernating myocardium harvested from nondialysis patients during coronary artery bypass surgery.[27,28]

The smaller number of regional wall motion abnormalities that occurred during biofeedback dialysis compared with standard HD suggests less segmental myocardial ischemia. Biofeedback dialysis works on the principle of a negative-feedback loop, designed to preserve blood volume to an extent that avoids hypotension.[19] Changes in UF rate and dialysate conductivity are made when relative blood volume decreases to less than a set limit, but, in theory, before BP decreases. Several studies showed that biofeedback dialysis decreased IDH frequency in patients who were both prone and resistant to IDH, and this also was confirmed by our results.[11,12] In our study, BP was significantly greater during biofeedback dialysis despite a trend toward greater UF volume. This greater BP appeared to

Table 5. Echocardiographic Measurements of Cardiac Dimensions at the Start and End of Dialysis

	Predialysis		End of Dialysis		
	HD	BFD	HD	BFD	*P*
Left ventricle major axis diastole (cm)	8.4 ± 1.1	8.2 ± 1.0	8.1 ± 0.8	8.0 ± 0.6	0.79
Left ventricle major axis systole (cm)	7.1 ± 1.3	7.1 ± 1.0	7.0 ± 1.0	6.9 ± 0.6	0.97
Left ventricle minor axis diastole (cm)	5.2 ± 1.0	5.2 ± 0.8	5.1 ± 1.1	5.4 ± 0.8	0.92
Left ventricle minor axis systole (cm)	4.6 ± 1.0	4.3 ± 1.3	4.5 ± 0.7	4.3 ± 0.9	0.9
Left atrium diameter (cm)	4.5 ± 0.7	4.5 ± 0.6	4.4 ± 0.6	4.4 ± 0.7	0.99
Left atrium indexed volume (mL/m^2)	33.0 ± 12.0	33.1 ± 11.0	30.5 ± 12.0	30.8 ± 11.0	0.95

NOTE. Left atrium volume was calculated by Simpson's rule from single plane (apical 4 chamber) and indexed for body surface area. There were no significant differences in any dimensions comparing the 2 dialysis modalities.

Abbreviation: BFD, biofeedback dialysis.

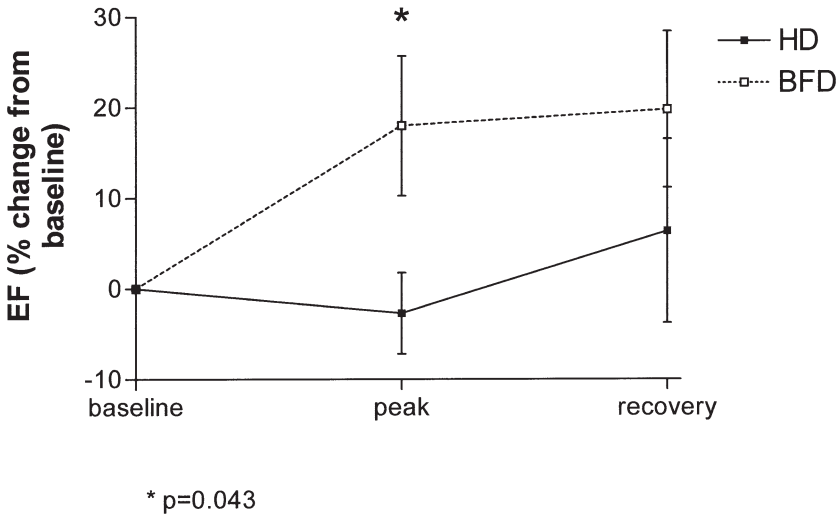


Fig 4. Global LV function (EF) during standard (HD) and biofeedback dialysis (BFD). Data expressed as mean ± SE.

be caused by a smaller decrease in stroke volume and cardiac output and a higher pulse rate during biofeedback dialysis. One possible explanation for the higher stroke volume and cardiac output during biofeedback dialysis is better preserved blood volume, leading to improved cardiac filling. Baroreflex sensitivity also was lower and showed less variability during biofeedback dialysis, indicating less autonomic activity. This implies less hemodynamic stress during biofeedback dialysis. The higher BP, fewer IDH episodes, and improved systemic hemodynamics all have the capacity to lessen episodes of myocardial hypoperfusion compared with standard HD.

The large number of new regional wall motion abnormalities seen in our patients may reflect their demographics. All were prone to IDH, all had LV hypertrophy, and 7 of 8 patients had documented atherosclerosis, although these are not uncommon findings in long-term dialysis patients. One weakness of our study is that patients did not undergo coronary angiography, which would have provided information about the degree and extent of large-vessel coronary disease to correlate with the echocardiographic data. However, there are plausible mechanisms other than large-vessel obstructive coronary disease that may predispose to myocardial hypoperfusion. Coronary flow reserve is dependent not only on large-vessel patency, but also on microvascular disease, which also decreases the ability to increase blood flow to myocardium during increased demand. Specific microvascular disease has been described in dialysis patients, likely because of the high prevalence of diabetes, hypertension, and vascular calcification.[29] In addition,

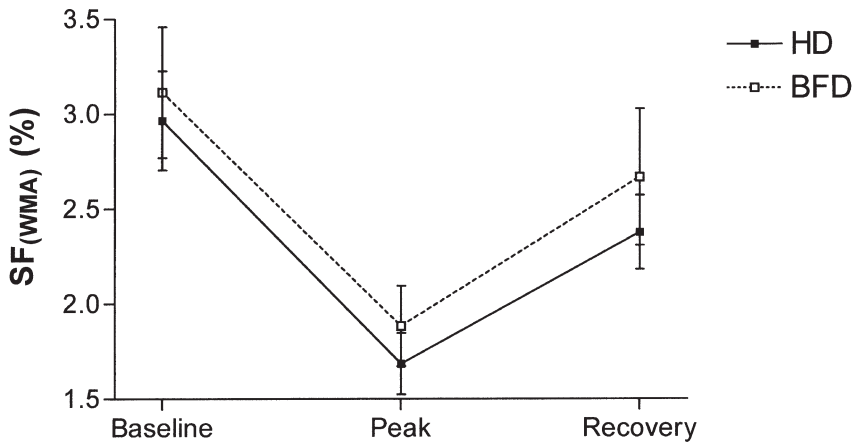


Fig 5. Mean regional LV function (SF) in regions that developed new regional wall motion abnormalities (RWMAs) during standard (HD) and biofeedback dialysis (BFD). Data expressed as mean ± SE.

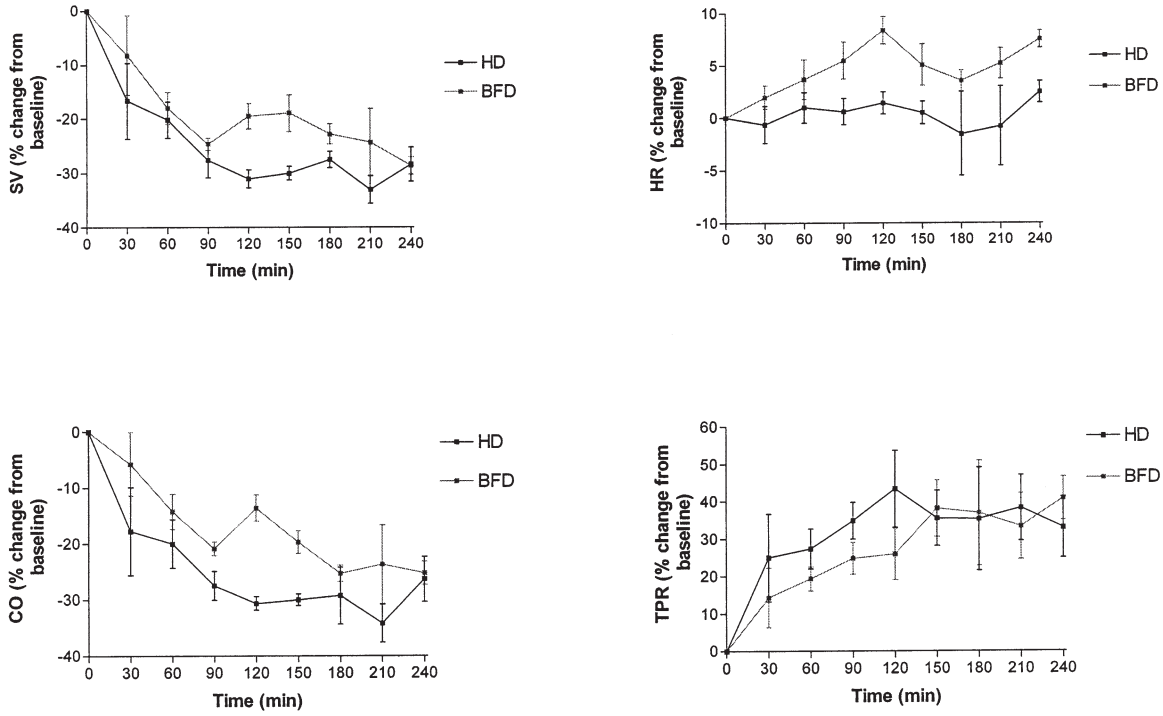


Fig 6. Systemic hemodynamics during standard (HD) and biofeedback (BFD) dialysis. During BFD, there was a greater increment in pulse ($P < 0.001$) and smaller decrease in stroke volume and cardiac output ($P < 0.001$ for each). As a result, peripheral resistance increased to a slightly lesser extent during BFD ($P < 0.05$).

acute severe stress can induce stunning despite normal coronary anatomy,[30] but although HD is associated with sympathetic activation and a hyperadrenergic state,[31,32] none of our patients had a phenotype that resembled acute severe stress. Finally, it is possible that the autonomic nervous system may affect ventricular function during dialysis. Altered autonomic function, which is a common finding in dialysis patients, affects both IDH frequency and ventricular contractility.[33,34] We observed differences in baroreflex sensitivity between dialysis modalities, but our current study did not assess the direct effect of the autonomic nervous system on LV dysfunction.

EF did not change significantly from baseline during either HD or biofeedback dialysis. However, there was a significant difference in percentage of change from baseline between dialysis modalities because of the trend for EF to decrease at peak stress with HD and increase with biofeedback dialysis. The trend for EF to increase with biofeedback dialysis despite the development of regional wall motion abnormalities was unexpected and occurred because SF in some unaffected LV regions increased during peak stress. This phenomenon also was seen during HD, but to a lesser extent. This corresponds to the better preservation of stroke volume and cardiac output during biofeedback dialysis. Again, the reasons behind these changes are not explained, but may suggest that in regions without ischemia, function increases in the short term in response to the hemodynamic stress of dialysis. Indexed left atrial volume is used as a marker for diastolic dysfunction.[14] Measuring diastolic function is not a primary objective of this study because myocardial stunning is defined on systolic function, and considerable controversy still surrounds assessments of diastolic function in dialysis patients. However, as may be expected with the high prevalence of LV hypertrophy, 5 of 8 patients had an indexed left atrial volume greater than 28 mL/m^2, implying a degree of diastolic dysfunction. However, there was no difference in this value or in mean indexed left atrial volume comparing HD and biofeedback dialysis either before or after dialysis.

Our study has some potential weaknesses. Patient numbers are small; thus, our results should be regarded as preliminary and need to be replicated in a larger number of patients. This is particularly pertinent because echocardiographic measurements always entail a degree of variability, even under optimal conditions. We used endocardial borders as the sole marker of abnormal contraction and therefore did not take account of wall thickening or transmyocardial heterogeneity. However, our method is repeatable and quantitative. Finally, ours was a short-term study; therefore, any effect of dialysis-induced regional wall motion abnormalities on long-term cardiac dysfunction is purely speculative at present.

In conclusion, this study shows that reversible myocardial dysfunction occurs during dialysis. Potentially, this could be a novel mechanism contributing to the excess of cardiovascular disease and cardiac failure seen in this patient group. In addition, we also show the occurrence is less during biofeedback dialysis, thereby suggesting that this phenomenon may be a target for intervention. Additional work is needed to confirm our findings, measure myocardial blood flow in conjunction with LV function, and study the long-term development of heart failure in response to repeated dialysis-induced myocardial stunning.

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