

# Effect of Hemodialysis on Left Ventricular Function

## DISSOCIATION OF CHANGES IN FILLING VOLUME AND IN CONTRACTILE STATE

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**ABSTRACT** Prior studies of the effect of hemodialysis on left ventricular function have not distinguished between the removal of uremic toxins and the change in cardiac filling volume. To separate these effects, left ventricular function was examined by serial echocardiography in five stable hemodialysis patients before and after three different dialysis procedures: (a) hemodialysis with volume loss, (b) ultrafiltration (volume loss only), and (c) hemodialysis without volume loss. The patients were similarly studied under control conditions and after increased (5° of head-down tilt for 90 min) and decreased (lower body negative pressure) cardiac filling volume.

After hemodialysis with volume loss, end-diastolic volume (EDV) decreased from 167 to 128 ml ( $P < 0.001$ ) and end-systolic volume (ESV) decreased from 97 to 51 ml ( $P < 0.001$ ) without a change in stroke volume (SV). Ejection fraction increased from 42 to 52% ( $P < 0.001$ ) and mean velocity of circumferential fiber shortening (VCF) increased from 0.61 to 1.04 circumferences (circ)/s ( $P < 0.001$ ). After ultrafiltration, EDV decreased from 167 ml to 124 ml ( $P < 0.001$ ) and SV from 73 ml to 39 ml ( $P < 0.001$ ), without significant changes in ESV or VCF. In contrast to the maneuvers in which volume loss occurred, after hemodialysis without volume loss ESV decreased from 95 to 66 ml ( $P < 0.001$ ) and SV increased from 74 ml to 97 ml ( $P < 0.001$ ) without changes in EDV. EF increased from 44 to 59% ( $P < 0.001$ ) and VCF increased from 0.64 to 1.26 circ/s ( $P < 0.001$ ). Ventricular function curves plotted from data obtained under conditions of altered cardiac filling volume before and after the three dialysis maneuvers demonstrate that ultrafiltration produced a pure Frank-Starling effect, while

hemodialysis with or without volume loss produced a shift in the ventricular function curves, which demonstrated an increase in the contractile state of the left ventricle. The changes in left ventricular function produced by regular hemodialysis are the combined effects of a decrease in EDV and an increase in the contractile state of the left ventricle.

### INTRODUCTION

The existence of a uremic cardiomyopathy has remained an important, but unsettled issue in clinical medicine. While experimental studies have shown that high concentrations of uremic compounds are capable of depressing cardiac function in vitro, the demonstration of a uremic cardiomyopathy has been lacking (1-3). Such a demonstration is hampered by the plethora of complicating diseases that prohibit the dissociation of the independent effects of uremia (4). The commonly associated conditions of coronary artery disease, hypertension, and pericardial disease may individually or in combination affect left ventricular performance and make the influence of uremia per se difficult to evaluate (5, 6).

One approach to the question of the existence of a uremic cardiomyopathy is to examine the acute effects of hemodialysis on left ventricular function. Earlier human studies of hemodynamic changes after hemodialysis in patients with chronic renal failure were confined to the demonstration of alterations in cardiac output, heart rate, systemic arterial pressure, and peripheral vascular resistance (7-11). The advent of non-invasive techniques has permitted a more comprehensive evaluation of left ventricular function in patients in chronic renal failure and of the effects of hemodialysis (12-17). Studies using systolic time intervals (12-14), echocardiography (14-16), and radionuclide

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angiography (17) have reached differing conclusions on the precise effect of hemodialysis on left ventricular function. Furthermore, in assessing the contractile state of the left ventricle in these noninvasive studies, the effect of altering cardiac filling volume was not taken into account (18).

The purpose of the present study was to separate the effects of changes in cardiac filling volume and of removal of uremic toxins on left ventricular function during hemodialysis. Furthermore, the patients were studied under conditions of altered cardiac filling volume to permit the determination of left ventricular function curves.

## METHODS

Five male patients, mean age  $53 \pm 2$  yr, who were undergoing regular hemodialysis for chronic renal failure volunteered for the study. Each individual had no clinical evidence of coronary artery disease. The only medications being taken by the individual patients were phosphate binders and vitamins; specifically, none of the patients were taking digoxin, beta blocking agents, or antihypertensive therapy. Details of the protocol were explained to each subject and informed written consent was obtained. The study protocol was approved by the Human Studies Committee at the Veterans' Administration Medical Center, Dallas.

Each of the patients was studied by echocardiography prior to and within 60 min of the completion of three different hemodialysis maneuvers. Also, to evaluate left ventricular function in each patient over a wide range of end-diastolic volumes, a series of controlled alterations in cardiac preload were carried out before and after each dialysis maneuver.

After the base-line echocardiographic studies, the patients underwent one of three dialysis maneuvers. The studies were conducted on usual dialysis days. The identical dialyzer systems (Travenol Hollow-Fiber 1.3 m<sup>2</sup> and Travenol RSD delivery system, Travenol Laboratories, Deerfield, IL) were used in each maneuver. The same sequence was followed irrespective of the hemodialysis maneuver performed.

Patients were weighed and needles for dialysis inserted; 15 min later, supine blood pressure, heart rate, and blood samples for serum electrolytes and plasma osmolality were obtained. The patients were recumbent for 3 h during each of the maneuvers.

The three different hemodialysis maneuvers were performed in random order and were as follows: (a) *Regular hemodialysis with weight loss*. Standard hemodialysis with positive pressure, dialysate sodium concentration of 132 meq/liter, weight loss of ~2% of body weight. (b) *Ultrafiltration only*. The dialysis machine was placed in bypass with positive pressure, dialysate was not circulated, weight loss of ~2% of body weight. (c) *Regular hemodialysis without weight loss*. No positive pressure, dialysate sodium concentration of 132 meq/liter.

Electrolyte determinations were analyzed by flame photometry and blood urea nitrogen, plasma bicarbonate, chloride, and creatinine were assayed by the autoanalyzer in the central hospital laboratory.

Echocardiograms were obtained by a two-dimensional, phased-array ultrasonograph (Varian V-3000, Varian Instruments, Palo Alto, CA). All studies were performed in the recumbent position with the transducer placed in the third,

fourth, or fifth intercostal space, depending on the size of the subject. An optimal short-axis circular or almost circular image at the widest point of the left ventricle below the tips of the mitral valve leaflets was centralized within the display arc and the M-mode cursor was directed across the left ventricular cavity at the widest point. M-mode tracings were recorded on a strip chart recorder. Use of the two-dimensional image and the cursor ensured that M-mode echocardiographic images were obtained from the same point in the left ventricular cavity despite any alterations in cardiac position produced by the interventions (19).<sup>1</sup>

Endocardial echoes of the left side of the interventricular septum and the posterior left ventricular wall were identified as suggested by Popp et al. (20). Measurements of left ventricular end-diastolic (EDD)<sup>2</sup> and end-systolic dimension (ESD) were made from each echocardiogram. Stroke dimension was determined as EDD-ESD and shortening fraction as EDD-ESD/EDD. Left ventricular end-diastolic volumes (EDV) and end-systolic volumes (ESV) were calculated according to Teichholz et al. (21), where volume = (diam)<sup>3</sup> × {7/4(2.4 + diam)} cm<sup>3</sup>. Mean velocities of circumferential fiber shortening were estimated by the method of Cooper and colleagues (22). Values for mean velocity of circumferential fiber shortening in our laboratory range from 0.67 to 1.59 circ/s, a somewhat lower range than those reported from other laboratories (23, 24). A separate study of five normal subjects in our laboratory has shown that the method of measuring left ventricular ejection time had no significant influence on the estimation of mean velocity of circumferential fiber shortening either during control studies or during variations in preload (25). Furthermore, a previous study in our laboratory showed similar estimations of cardiac output by echocardiography to those determined by the acetylene rebreathing technique (26).

Echocardiographic measurements were made separately by two investigators without prior knowledge of the subjects' circumstances. In each subject, a minimum of three cardiac cycles was analyzed during expiration and the measurements averaged. Each measurement used was the mean of two observers. Previous studies of resting subjects by the same investigators have shown minimal interobserver variability (EDD:  $r = 0.97$ , SEE = 0.12 cm; ESD:  $r = 0.96$ , SEE = 0.13 cm) and interobserver variability (EDD:  $r = 0.99$ , SEE = 0.07; ESD:  $r = 0.98$ , SEE = 0.10 cm). These latter data represent an overall intraobserver variability of left ventricular dimensions of  $1.9 \pm 0.4\%$ , which compares favorably with data from other laboratories (19, 27).

The heart rate was obtained from a simultaneous electrocardiographic recording. Blood pressure readings were obtained at 1-min intervals throughout each intervention by a Narco Bio-Systems, Inc., Houston, TX programmed electrophygmomanometer and recorded on a strip chart recorder. Previous studies have demonstrated good agreement between these studies and auscultatory readings (26, 28). Mean arterial pressure was calculated as diastolic pressure plus one-third of the pulse pressure.

*Experimental protocol.* The following protocol previously shown to significantly increase and decrease left ventricular preload was also carried out (25). Echocardiograms

<sup>1</sup> Smucker, M. L., S. S. Cassidy, and J. V. Nixon. Submitted for publication.

<sup>2</sup> *Abbreviations used in this paper:* circ, circumference; EDD, end diastolic dimension; EDV, end diastolic volume; ESD, end systolic dimension; ESV, end systolic volume; LBNP, lower body negative pressure; SV, stroke volume; VCF, velocity of circumferential fiber shortening.

were obtained before and at the termination of each preload variation. All the following studies were performed in the supine position at the same time of day according to the following protocol: (a) Base-line studies were carried out after a rest period of 15 min. (b) Increase in preload was produced by 5° of head-down tilt. Data were recorded after 90 min of tilt, the time of maximal effect of this intervention on the dimensional measurements of the left ventricle according to previous studies in our laboratory (26). Head-down tilt at this angle produces a transient increase in central venous pressure of ~2.5 cm of water, but with a return to base line at the time the left ventricle reaches its maximal size. (c) Repeat base-line studies were carried out after a rest period of ~15 min. (d) Decrease in preload was induced by a gradual application of lower body negative pressure (LBNP) to -40 mmHg in the supine position; pressure was lowered in increments of -8, -16, -32, to -40 mmHg at intervals of 1, 3, and 3 min, respectively. Data were recorded during the last 15 s of the 5-min application of LBPN at -40 mmHg. Details of the LBPN protocol and the device have been published elsewhere (28-30). LBPN of this magnitude produces venous pooling with a progressive increase in leg volume of 500-700 ml and a similar or slightly larger reduction in circulating blood volume. Central venous pressure decreases by ~5 cm of water. The order of procedures b and d were allocated at random.

Data obtained before and at the termination of each intervention were compared and significant differences determined by analysis of variance for single factor experiments having repeated measures (31). When significant differences ( $P < 0.05$ ) between groups were found, within-group differences were determined by the Student-Newman-Keuls multiple range test and values of  $< 0.05$  were considered significant. Power curves and linear regression equations were determined from individual values of stroke volumes and end-diastolic volumes to obtain left ventricular function curves (for  $r > 0.56$ ,  $P < 0.01$ ).

## RESULTS

The changes in body weight, creatinine, sodium, potassium, bicarbonate, and chloride levels are summarized in Table I and are as one would anticipate. The changes in left ventricular dimensions, shortening fraction, mean velocity of circumferential fiber short-

ening (VCF), heart rate, and blood pressures are summarized in Table II. There were no significant differences in base-line values obtained before the different dialysis maneuvers.

After regular hemodialysis (volume loss and dialysis), mean body weight was decreased from  $81.7 \pm 2.3$  kg to  $79.4 \pm 2.1$  kg ( $P < 0.01$ ), and serum creatinine levels from  $21.3 \pm 3.3$  mg/dl to  $12.1 \pm 1.4$  mg/dl ( $P < 0.001$ ) (Table I). Mean left ventricular EDV decreased by 23% from  $167 \pm 11$  cm<sup>3</sup> to  $128 \pm 11$  cm<sup>3</sup> ( $P < 0.001$ ), and mean ESV by 37% from  $97 \pm 7$  cm<sup>3</sup> to  $61 \pm 5$  cm<sup>3</sup> ( $P < 0.001$ ) (left panel, Fig. 1). Mean ejection fraction increased by 26% from  $0.42 \pm 0.03$  to  $0.52 \pm 0.2$  ( $P < 0.001$ ) and mean VCF by 66% from  $0.61 \pm 0.6$  circ/s to  $1.04 \pm 0.1$  circ/s ( $P < 0.001$ ). Mean EDD decreased from  $5.8 \pm 0.2$  to  $5.2 \pm 0.2$  cm and mean ESD from  $4.6 \pm 0.1$  to  $3.8 \pm 0.1$  cm (Table II). No significant changes occurred in stroke volume, heart rate, or mean blood pressure.

Individual data obtained at rest and during head-down tilt and LBPN, both before and after dialysis, relating stroke volume (SV) to EDV were compared to obtain left ventricular function curves. The data in each experimental circumstance conform to a normal left ventricular function curve, but never significantly different from the linear regression. Each patient provided four data points from each function curve obtained from echocardiograms recorded before and during head-down tilt and before and during LBPN. Regular hemodialysis caused a leftward shift of the left ventricular function curve (right panel, Fig. 1).

After ultrafiltration (volume loss only), mean body weight was reduced from  $81.4 \pm 1.9$  to  $78.8 \pm 2.0$  kg ( $P < 0.005$ ) while serum creatinine levels did not change significantly (Table I). Mean EDV decreased by 26% from  $167.9$  cm<sup>3</sup> to  $124 \pm 6$  cm<sup>3</sup> ( $P < 0.001$ ) and mean SV by 47% from  $73 \pm 6$  to  $39 \pm 5$  cm<sup>3</sup> ( $P < 0.001$ ) (left panel, Fig. 2). Mean ejection fraction also decreased

TABLE I  
Body Weights and Serum Creatinine, Sodium, Potassium, Bicarbonate, and Chloride Levels before (Pre) and after (Post) the Three Different Dialysis Maneuvers ( $n = 5$ ; Mean  $\pm$  SE)

	Regular dialysis with volume loss		Ultrafiltration		Regular dialysis without volume loss	
	Pre	Post	Pre	Post	Pre	Post
Weight, kg	$81.7 \pm 2.3$	$79.4 \pm 2.1^*$	$81.4 \pm 1.9$	$78.9 \pm 2.0^*$	$79.9 \pm 2.0^*$	$79.9 \pm 2.1$
Creatinine, mg/dl	$21.3 \pm 3.3$	$12.1 \pm 1.4^*$	$18.7 \pm 2.2$	$18.4 \pm 2.1$	$20.3 \pm 2.9$	$11.3 \pm 1.8$
Sodium, meq/liter	$142 \pm 1.3$	$142 \pm 1.1$	$140 \pm 1.1$	$140 \pm 1.1$	$140 \pm 1.2$	$136 \pm 1.2^*$
Potassium, meq/liter	$5.2 \pm 0.4$	$3.9 \pm 0.1^*$	$4.7 \pm 0.3$	$4.7 \pm 0.3$	$5.0 \pm 0.5$	$3.6 \pm 0.2^*$
Bicarbonate, meq/liter	$17 \pm 2$	$22 \pm 1^*$	$19 \pm 2$	$19 \pm 2$	$17 \pm 2$	$22 \pm 1$
Chloride, meq/liter	$101 \pm 2$	$99 \pm 2$	$101 \pm 2$	$101 \pm 1$	$100 \pm 2$	$96 \pm 1$

No significant differences between predialysis data.

\* Predialysis vs. postdialysis,  $P < 0.05$ .

TABLE II  
*Ventricular Dimensions, Shortening Fraction, Mean VCF, Heart Rate and Mean Blood Pressure before (Pre) and after (Post) the Three Different Dialysis Maneuvers*

	Regular dialysis with volume loss		Ultrafiltration		Regular dialysis without volume loss	
	Pre	Post	Pre	Post	Pre	Post
Weight, kg	81.7±2.3	79.4±2.1*	81.4±1.9	78.8±2.0*	79.9±2.1	79.8±2.1
Creatine, mg/dl	21.3±3.3	12.1±1.4*	18.7±2.1	18.4±2.1	20.3±2.9	11.3±1.8*
EDD, cm	5.8±0.2	5.2±0.2*	5.8±0.1	5.1±0.1*	5.8±0.1	5.7±0.1
ESD, cm	4.6±0.1	3.8±0.1*	4.5±0.1	4.3±0.1	4.5±0.1	3.9±0.1*
Shortening fraction	0.21±0.02	0.27±0.02*	0.22±0.01	0.15±0.02*	0.22±0.01	0.32±0.03*
Mean VCF, circ/s	0.61±0.06	1.04±0.1*	0.65±0.04	0.43±0.05	0.64±0.06	1.26±0.14*
Heart rate, beats per min	77±4	83±7	76±2	75±3	77±5	82±6
Mean BP, mmHg	126±6	122±4	116±5	115±3	124±3	117±3

No significant differences between predialysis data.

\* Predialysis vs. postdialysis,  $P < 0.05$ .

BP, blood pressure.

by 39% from  $0.44 \pm 0.02$  to  $0.31 \pm 0.03$  ( $P < 0.001$ ). Mean EDD decreased from  $5.8 \pm 0.1$  to  $5.1 \pm 0.1$  cm and mean ESD from  $4.5 \pm 0.1$  to  $4.3 \pm 0.1$  cm (Table II). No significant changes occurred in ESV, mean VCF, heart rate, or mean blood pressure. Ultrafiltration caused a movement downward on the same left ventricular function curve (right panel, Fig. 2).

After dialysis without volume loss, mean serum creatinine levels were reduced from  $20.3 \pm 2.9$  mg/dl to  $11.3 \pm 1.8$  mg/dl ( $P < 0.001$ ) (Table I). Mean ESV de-

creased by 24% from  $95 \pm 6$  to  $66 \pm 8$  cm<sup>3</sup> ( $P < 0.001$ ). Mean SV increased by 28% from  $74 \pm 6$  to  $94 \pm 7$  cm<sup>3</sup> ( $P < 0.001$ ), ejection fraction by 35% from  $0.44 \pm 0.03$  to  $0.59 \pm 0.04$  ( $P < 0.001$ ), and mean VCF by 96% from  $0.64 \pm 0.06$  circ/s to  $1.26 \pm 0.14$  circ/s ( $P < 0.001$ ) (left panel, Fig. 3). Mean EDD decreased from  $5.8 \pm 0.1$  to  $5.7 \pm 0.1$  cm and mean ESD from  $4.5 \pm 0.1$  to  $3.9 \pm 0.1$  cm (Table II). No significant changes occurred in mean body weight, left ventricular EDV, heart rate, or mean blood pressure. The hemodialysis without volume loss

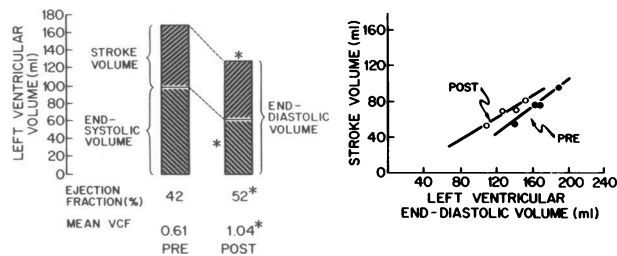


FIGURE 1 Left panel: Changes in left ventricular EDV, ESV, and SV, ejection fraction and mean velocity of VCF (circ per second) before (PRE) and after (POST) regular hemodialysis with weight loss. Asterisks represent significant changes in mean values. Right panel: Relationships between left ventricular SV and EDV at supine rest, during head-down tilt and during LBNP before (PRE) and after (POST) regular hemodialysis with weight loss. The mean regression lines represent the equations  $SV = 0.64EDV - 35$  ( $r = 0.88$ ) (predialysis) and  $SV = 0.6EDV - 12$  ( $r = 0.93$ ) (postdialysis), neither significantly different from the power curves  $SV = 14.6EDV^{0.01}$  ( $r = 0.89$ ) (predialysis) and  $SV = 17.1EDV^{0.01}$  ( $r = 0.92$ ) (postdialysis). The regression lines are plotted from all the individual patients' data; mean values at supine rest and during each altered preload state are shown as closed circles before and open circles after each dialysis maneuver.

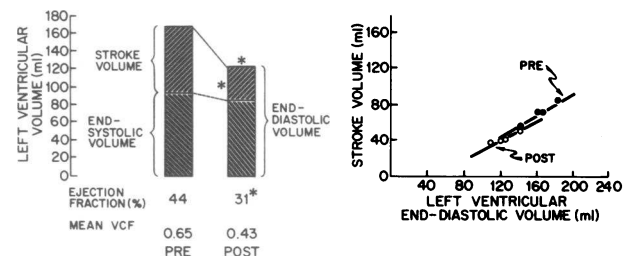


FIGURE 2 Left panel: Changes in left ventricular EDV, ESV, and SV, ejection fraction and mean VCF (circ/second) shortening before (PRE) and after (POST) ultrafiltration only. Asterisks represent significant changes in mean values. Right panel: Relationships between left ventricular SV and EDV at supine rest, during head-down tilt and during LBNP before (PRE) and after (POST) ultrafiltration only. The linear regression lines represent the equations  $SV = 0.6EDV - 30$  ( $r = 0.86$ ) (predialysis) and  $SV = 0.54EDV - 25$  ( $r = 0.83$ ) (postdialysis), neither significantly different from the power curves  $SV = 14.0EDV^{0.01}$  ( $r = 0.85$ ) (predialysis) and  $SV = 8.3EDV^{0.01}$  ( $r = 0.85$ ) (postdialysis). The regression lines are plotted from all the individual patients' data; mean values at supine rest and during each altered preload state are shown as closed circles before and open circles after each dialysis maneuver.

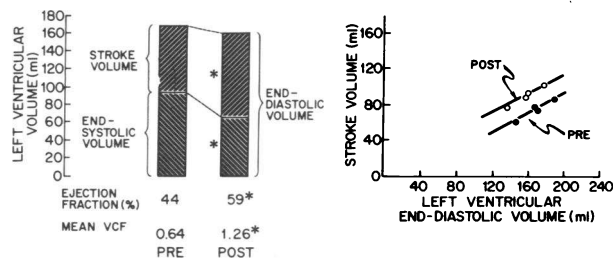


FIGURE 3 Left panel: Changes in left ventricular EDV, ESV, and SV, ejection fraction and mean VCF (circ per second) before (PRE) and after (POST) regular hemodialysis without weight loss. Asterisks represent significant changes in mean values. Right panel: Relationships between left ventricular SV and EDV at supine rest, during head-down tilt and during LBNP before (PRE) and after (POST) regular hemodialysis without weight loss. The linear regression lines represent the equations  $SV = 0.56EDV - 20$  ( $r = 0.81$ ) (predialysis) and  $SV = 0.51EDV + 10$  ( $r = 0.56$ ) (postdialysis), neither significantly different from the power curves  $SV = 19.4EDV^{0.01}$  ( $r = 0.82$ ) (predialysis) and  $SV = 31.9EDV^{0.01}$  ( $r = 0.57$ ) (postdialysis). The regression lines are plotted from all the individual patients' data; mean values at supine rest and during each altered preload state are shown as closed circles before and open circles after each dialysis maneuver.

caused an upward shift of the left ventricular function curve.

## DISCUSSION

Cardiac involvement in chronic renal failure is well described. While some investigators have had difficulty documenting a specific cardiomyopathy, others have described several cardiac and associated abnormalities, including pericarditis, hypertension, hypervolemia, anemia, electrolyte disturbances, coronary artery disease, arrhythmias, cardiac failure, and electrolyte abnormalities (4-6, 32-34). Experimental studies have confirmed that impaired left ventricular function may be produced by the presence of circulating uremic toxins or the effect of vitamin D deficiency on sarcoplasmic reticulum and calcium transport (2, 35).

The assessment of changes in cardiac performance produced by hemodialysis was previously limited by the necessity to place arterial and venous catheters to measure hemodynamics. Measurement of cardiac output by indicator dye dilution or from plasma volume changes produced variable results (17, 18). While Goss et al. (7) reported a reduction in cardiac output, subsequent studies after hemodialysis by DelGreco et al. (8) showed a fall in cardiac output in patients without congestive heart failure compared to an increased cardiac output in patients with associated congestive heart failure.

The more recent advent of noninvasive techniques has permitted the reevaluation of previous studies and a more detailed examination of left ventricular function before and after hemodialysis. Studies using systolic time intervals have shown that hemodialysis consistently produces a reduction in left ventricular ejection time, concluding that hemodialysis reduces stroke volume (12, 13). Conclusions regarding changes in contractility were variable, Bornstein et al. (13) showing an increase in prejection period, while Prakash and Wegner (12) showed no change in this interval. Hung and associates (17) used radionuclide-determined left ventricular ejection fractions to show that while the ejection fractions of patients with associated congestive heart failure increased, hemodialysis produced no significant changes in those without heart failure. They concluded that the improvement in cardiac function as measured by ejection fraction was due to circulating blood volume changes rather than alterations in myocardial contractility.

The value of echocardiography in serially evaluating changes in left ventricular function during acute interventions is well accepted. The calculation of left ventricular volumes is based on the assumption that the left ventricle is always ellipsoid in shape and the minor diameter is always half the major diameter (19, 21, 25). It is possible that at the extremes of ventricular volumes encountered in our patients the ventricle altered its shape, becoming more ellipsoid at small volumes and more spherical at higher volumes. The regression equation of Teichholz et al. (21) was derived from a series of angiographically normal ventricles over a wider range of volumes than those encountered in our patients during the various interventions. Furthermore, estimations of ventricular volumes in all types of cardiac disease by two-dimensional echocardiography have shown a better correlation with angiography (36-39). However, the linear dimensional changes are identical to the volume changes, the regression equation used is valid over the ranges of ventricular volumes of our patients, and the existence of clinical evidence of coronary artery disease excluded patients from our study. Thus, any intrinsic error in volume estimations would apply consistently to comparative values and confirms that the changes seen in our patients are real rather than artificial.

It would appear that echocardiography is ideal for the direct measurement of changes in left ventricular function caused by hemodialysis of patients in chronic renal failure. Although several investigators have demonstrated significant reductions in left ventricular EDV and ESV, changes in SV, ejection fraction and contractile state, as measured by mean VCF, have differed (15, 16, 40). The data obtained from the patients in our study resolve several of these differences.

Furthermore, by using three different forms of dialysis, it has been possible to separate the effects of changes in cardiac filling volume and the removal of uremic toxins on left ventricular function. The reduction in EDV produced by regular hemodialysis is consistent with previous reports (15, 16, 40). It has been well established in both experimental and human studies that changes in EDV are produced by alterations in circulating blood volume, and thus cardiac preload, to produce a Frank-Starling response that is independent of changes in left ventricular contractility. (25, 26, 28, 41-43). Furthermore, changes induced by the Frank-Starling mechanism result in proportional changes in SV (40, 41). The lack of significant change in mean EDV after hemodialysis without plasma volume loss in the same patients confirms these conclusions.

ESV has been shown to be useful in differentiating changes in the contractile state of the left ventricle from changes induced by the Frank-Starling mechanism (41, 42, 44). Furthermore, changes in ESV are inversely proportional to changes in ejection fraction (41, 42). Thus, the combination of reduction in ESV with increases in ejection fraction and mean VCF in our patients undergoing regular hemodialysis suggest an increase in the contractile state. However, previous studies of normal subjects in our laboratory have shown that although mean VCF remains unchanged, both ESV and ejection fraction are affected by wide variations in cardiac preload (25). These latter findings would appear to be confirmed by the data obtained from the patients undergoing hemodialysis by ultrafiltration, who showed a minimal but significant reduction in ESV and a significant reduction in ejection fraction without a change in mean VCF. After hemodialysis without volume loss, the significant increase in mean VCF was accompanied by proportional changes in ESV and ejection fraction similar to those found after regular hemodialysis. These findings indicate that the changes in ESV induced by hemodialysis are in fact produced by an increase in contractile state of the left ventricle independent of an alteration in cardiac filling volume.

Mean VCF is the most widely accepted clinical echocardiographic measurement of myocardial contractile state (45, 46). It is noteworthy that the predialysis values for mean VCF are consistently below the normal range of values for our laboratory (Table II). The significant increase in mean VCF seen in our patients after regular hemodialysis concurs with the previous reports of Fernando et al. (15) and McDonald et al. (40). However, the studies of Fernando and colleagues showed significant changes in mean arterial pressure and those of McDonald and associates showed significant changes in heart rate. Previous studies of

normal individuals have shown that mean VCF is insensitive to changes in preload but that acute alterations in heart rate and blood pressure produce changes in this measurement (26, 47-49). In the present study the three hemodialysis maneuvers did not produce significant changes in either heart rate or systemic arterial pressure. The significant increase in mean VCF after hemodialysis without volume loss, combined with the changes in ESV during regular hemodialysis, confirms that the increase in mean VCF after regular hemodialysis reflects a real increase in the contractile state of the left ventricle. In the case of our patients, this increase merely represents a return to normal function from a severely impaired functional predialysis state.

The changes in left ventricular function curves produced by the three different hemodialysis maneuvers used in this study support the conclusions drawn from the changes in mean VCF and ESV. After ultrafiltration, the removal of volume causes a movement downward on the same left ventricular function curve indicating a pure Frank-Starling effect without a change in the contractile state of the left ventricle (right panel, Fig. 2). Following hemodialysis without volume loss, the removal of uremic toxins causes an upward shift of the ventricular function curve indicating an increase in the contractile state with no change in the Frank-Starling effect (right panel, Fig. 3). After regular hemodialysis, the volume loss and the removal of uremic toxins causes a leftward shift of the ventricular function curve indicating an increase in the contractile state with a decrease in the Frank-Starling effect (right panel, Fig. 1). While delineating the detail of the hemodynamic responses to dialysis, it is clear that this study does not address the issue of the mechanisms responsible for the improvement on left ventricular function. Further studies analyzing the effects of calcium or bicarbonate changes during hemodialysis may help to answer this question.

In summary, the results of our study separate the effects of volume removal from dialysis per se on left ventricular function in stable patients with end-stage renal disease. The possible mechanisms responsible for the positive inotropic effect of dialysis per se are not resolved by these studies. Consideration of the effects of uremic toxin removal and calcium or bicarbonate changes are worthy of further investigation.

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