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Left Ventricular Mechanics and Contractile State in Children and Young Adults With End-Stage Renal Disease: Effect of Dialysis and Renal Transplantation

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The potential existence of a specific uremia-associated myocardial depressant factor was explored by evaluating nine pediatric subjects (3 to 21 years) without evidence of coronary artery disease or long-standing hypertension 1) before entering a dialysis program, 2) while undergoing a long-term dialysis regimen, and 3) after successful renal transplantation. Myocardial contractility was quantitated with load-independent indexes using the end-systolic pressure-dimension relation (Emax) and the relation of rate-corrected velocity of shortening to end-systolic wall stress. Myocardial loading status was determined by the direct measurement of afterload (end-systolic wall stress) and the functional quantitation of preload (differences between the relation of fractional shortening and velocity of shortening to end-systolic stress).

Most patients (55%) were found to have abnormal ejection phase indexes of ventricular function either before or after entry into dialysis. However, contractility was normal in all subjects at each of their evaluations, and no change in contractility was found after dialysis or transplantation. Loading status was highly variable and usually abnormal before transplantation and accounted entirely for the abnormalities of fractional shortening and velocity of shortening. Transplantation invariably resulted in normalization of loading status and ejection phase indexes of ventricular function.

In these children and young adults with uremia, abnormal ejection phase indexes of ventricular function were frequent and caused by associated abnormalities in ventricular loading. Contractility, however, was normal and no evidence of a uremia-associated myocardial depressant was found.

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Cardiovascular abnormalities, including congestive heart failure, occur frequently in patients with renal failure. Abnormal left ventricular systolic function has been observed in some patients (1–7), leading to speculation that uremia causes myocardial dysfunction, either directly through circulating toxins (8–11) or secondarily through associated metabolic abnormalities such as hypocalcemia or hypermagnesemia (12,13). Improved ventricular function after dialysis or transplantation has also been interpreted as evidence for a specific uremia-associated cardiomyopathy (14–22). However, the implications of these findings concerning myocardial contractility are obscured by the fact that ventricular function has invariably been evaluated using ejection phase indexes of left ventricular performance such as ejection fraction or systolic time intervals. These indexes are known to be highly sensitive to left ventricular loading conditions (23–27), which are usually abnormal in uremic patients and change radically with dialysis or renal transplantation. Therefore, uncertainty remains as to whether the observed abnormalities are secondary to depressed contractility or altered loading conditions.

The recent development and validation of load-independent indexes of left ventricular contractility enable reconsideration of this issue. In particular, building on a series of observations in the isolated heart, the end-systolic pressure-volume or pressure-diameter relation (Emax) has been shown to be both sensitive to contractile state and independent of loading conditions within the physiologic range (26,28,29). The clinical usefulness of this index has been demonstrated, and noninvasive methods for its determination have been developed (30). In addition, we have recently described a method of force-velocity analysis whereby al-

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terations in afterload, preload and contractility can be distinguished (27). These methods were applied to a group of children and young adults with end stage renal disease to determine the range of left ventricular mechanics and contractile state found in these patients and the effect of dialysis or renal transplantation, or both. Because we specifically wished to evaluate the effects of the uremic state, a young and otherwise healthy group of subjects was selected to avoid the potential confounding effects of coronary artery disease or long-standing hypertension, as would be found in older subjects. Finally, because acute alterations in electrolyte status or fluid balance may directly alter contractile state or elicit autonomic reflexes that secondarily affect inotropic state, all evaluations were performed at least 24 hours after interventions such as dialysis or transfusions.

Methods

Study subjects (Table 1). The study group consisted of nine patients aged 3 to 21 years (mean 9.9) with end stage renal disease. The duration of chronic renal failure (defined as a serum creatinine concentration >3 mg/dl) was from 1 to 4 years. Two subjects had hypertension that was controlled with medical therapy (Patient 8 received captopril, and Patient 2 was treated with clonidine and hydralazine). All subjects were free of any evidence of structural heart disease on the basis of physical examination and evaluation with two-dimensional and Doppler echocardiography. Six subjects were first evaluated before entering the dialysis program, with repeat evaluation 2 to 6 months after stabilization on long-term dialysis. Three of these patients subsequently underwent successful renal allograft transplantation and were studied again 1 to 3 months later. Three additional patients were first studied after entering long-term dialysis and were reevaluated 2 to 4 months after successful renal transplantation. Altogether, therefore, data were available for six patients before and after dialysis and for six patients before and after transplantation. Afterload augmentation was not performed in one subject presenting with congestive heart failure, so that Emax data are available before and after dialysis in five subjects and before and after transplantation in five subjects.

Postdialysis evaluation. All patients were evaluated 24 to 48 hours after a dialysis session, except for Patient 9, who was treated with long-term peritoneal dialysis. The dialysate used was the same for all subjects, consisting of 3.5 mEq/liter of calcium, 2.0 mEq/liter of potassium and 36 mEq/liter of acetate with no bicarbonate. Serum calcium was normal in all subjects before dialysis (Table 1). Weight loss during dialysis varied from 1 to 9% of body weight.

Data recordings. Data were collected using previously reported methods (27). Echocardiograms were obtained using a Hewlett-Packard 77020A two-dimensional ultrasound system with two-dimensional–directed M-mode capabilities. High speed (100 mm/s) hard copy M-mode echocardiograms were obtained of the left ventricular minor axis with simultaneous phonocardiogram, electrocardiogram and indirect carotid pulse tracing. The phonocardiogram was recorded at the right upper sternal border, and simultaneous M-mode recording of aortic valve closure was made to permit positive identification of the aortic component of the second heart sound. A Dinamap 845 vital signs monitor (Critikon, Inc.) was used to obtain peak systolic and diastolic blood pressure measurements. Long- and short-axis two-dimensional echocardiographic views of the left ventricle were obtained for evaluation of regional wall motion.

After baseline recordings, 0.01 mg/kg body weight of intravenous atropine was given to prevent reflex bradycardia. A continuous 15 μg/kg per min intravenous infusion of the pure alpha-adrenergic agonist methoxamine was then initiated, and repeat data recordings were obtained every 1 to 2 minutes during a gradual increase in peak systolic pressure to 30 to 60 mm Hg over baseline. The infusion was then discontinued, and repeat recordings were obtained until baseline conditions were restored. Total infusion time

Table 1. Patient Profile, Serum Electrolytes and Body Mass Change During Dialysis

Patient No.	Age (yr)	CRF (yr)	Medications	Ca (mEq/liter)	K (mEq/liter)	Body Mass (kg)	
						Pre	Post
1	5	2		9.9	5.2	12.7	12.4
2	21	1	Clonidine, hydralazine	9.5	5.0	61.6	59.9
3	19	4	Phenytoin, furosemide	8.4	4.7	48.8	47.2
4	7	1		10.6	5.3	14.6	14.1
5	13	3		9.0	5.8	26.0	24.0
6	9	2	Captopril	10.4	4.0	32.3	29.2
7	15	2		NA	NA	NA	NA
8	17	14	Phenobarbital	NA	5.2	48.9	48.2
9	3	2		8.9*	5.5*	13.5*	

*Data obtained while the patient was undergoing long-term peritoneal dialysis. CA = serum calcium; CRF = duration of chronic renal failure; K = serum potassium; NA = not available; Post = after dialysis; Pre = before dialysis.

ranged from 7 to 16 minutes, and time to restoration of baseline conditions was 15 to 28 minutes.

Data analysis. High quality tracings from each subject were selected for computer analysis on a Franklin Quantic 1200 echocardiographic review station (Bruce Franklin, Inc.). This device has a digitizing pad with a sampling rate of 80 points/cm, giving a net digitizing rate of 800 points/s. In addition to baseline recordings, tracings for each subject were selected after atropine and during methoxamine infusion over a range of blood pressure values for calculation of Emax. Recordings with heart rate variation of more than 10 beats/min from the postatropine values were not used for Emax calculation.

The carotid pulse tracing as well as the left ventricular echocardiogram including the endocardial septal surface and the endocardial and epicardial borders of the left ventricular posterior wall were digitized. The carotid pulse tracing was corrected for time delay by electronically aligning the dicrotic notch with the aortic valve component of the second heart sound. From the digitized data, the following instantaneous measurements were derived by averaging three to five cardiac cycles: 1) left ventricular pressure throughout ejection, determined by linear interpolation of the instantaneous points of the carotid pulse tracing as previously described (27)—this method has been validated against an intraarterial standard in our laboratory (31); 2) left ventricular internal diameter; 3) left ventricular posterior wall thickness; and 4) left ventricular wall stress calculated according to the angiographically validated formula (32):

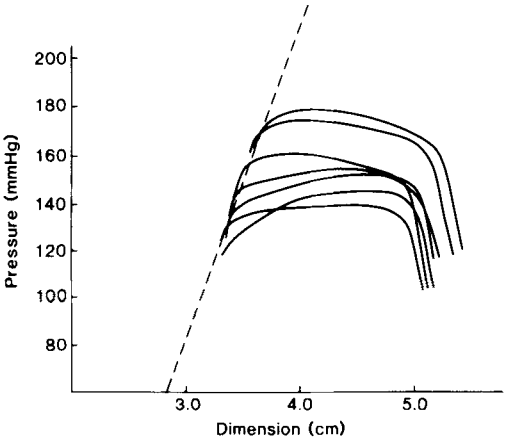
$$WS = \frac{(P)(D)(1.35)}{(h)(1 + [h/D])(4)},$$

where WS = wall stress (g/cm^2), P = pressure (mm Hg), D = dimension (cm), h = posterior wall thickness (cm) and 1.35 is the conversion factor from mm Hg to g/cm^2.

Wall stress, velocity of shortening and fractional shortening relations. End-diastolic measurements were taken at the time of maximal left ventricular dimension, and end-systolic measurements were taken at the time of aortic valve closure. Left ventricular ejection time was measured from the simultaneous carotid pulse tracing and adjusted to a heart rate of 60 beats/min by dividing by the square root of the RR interval. The left ventricular percent fractional shortening was calculated as the difference between the dimensions at end-diastole and end-systole divided by end-diastolic dimension. The rate-adjusted mean velocity of shortening was calculated by dividing fractional shortening by the rate-adjusted ejection time. End-diastolic dimension index was calculated by dividing end-diastolic dimension by the cube root of body surface area. The relation of fractional shortening and rate-adjusted velocity of shortening to end-systolic wall stress was calculated for each individual from tracings obtained under baseline conditions, and the mean values for these indexes were obtained for each of the four groups. The individual and group values for the relation of end-systolic wall stress to rate-adjusted velocity of shortening and end-systolic wall stress to fractional shortening were then compared with the previously reported normal values for these indexes in our laboratory (27).

Calculation of Emax. The relation of instantaneous pressure to left ventricular internal dimension throughout ejection at numerous levels of blood pressure during methoxamine infusion was calculated, and the appropriate value for each curve was selected for calculation of Emax. As illustrated in Figure 1, aortic valve closure occurs after the point in systole when the pressure/dimension ratio is maximal. This is a result of the period of time after cessation of anterograde flow into the aorta and before aortic valve closure (known as the "hang out" interval) during which pressure continues to decrease but ventricular volume is static (33). As discussed by Sagawa (28), the time of maximal elastance (that is, the maximal pressure:dimension ratio in isovolumic contractions) occurs earlier in the cardiac cycle. Therefore, calculation of Emax was performed using the value at which the pressure/dimension ratio attained its maximal value, rather than the time of aortic valve closure, which was used for the end-systolic measurements discussed previously. For each Emax determination, 6 to 12 points were used to fit an equation of the form: P = mD + b, using simple linear regression (least squares method), where P = pressure, m = slope, D = dimension, and b = Y intercept. The X intercept (that is, the X value when P = 0) was calculated and the slope and X intercept of this line were normalized to the cube root of body surface area to determine Emax and X intercept, respectively (30).

Figure 1. Examples of systolic pressure-dimension curves (from the time of onset of aortic ejection to the time of aortic valve closure) generated at several levels of arterial pressure during methoxamine infusion in one subject. The **upper left corner of each curve** (maximal pressure-dimension ratio) is determined, and the best linear fit (**dotted line**) is calculated. The slope of this line and the X axis intercept are adjusted for the cube root of body surface area to obtain Emax and the X-intercept, respectively.



Statistical analysis. Data are reported as mean ± 1 standard deviation unless otherwise noted. Comparisons between pre- and post-dialysis and pre- and posttransplantation were performed using the *t* test for paired data, with a probability (p) value <0.05 considered to be statistically significant.

Results

Blood chemistry data. Clinical, hemodynamic and echocardiographic data for each subject are presented in Tables 1 and 2. Hematocrit was not significantly higher in the postdialysis group compared with predialysis status. However, there was a significant increase in hematocrit after renal transplantation. Blood area nitrogen was significantly lower after dialysis compared with predialysis conditions, and both blood urea nitrogen and creatinine were significantly lower after transplantation. All subjects had normal values for blood urea nitrogen and creatinine at the time of evaluation after transplantation. Although large changes were noted in some individuals, blood pressure in the group was not significantly different after dialysis or transplantation.

Left ventricular dimensions and function (Fig. 2). Dimension at end-diastole tended to be lower after dialysis, but did not attain statistical significance. End-systolic dimension, fractional shortening, and rate-adjusted velocity of shortening were not significantly different after dialysis, although large individual changes were noted. In contrast, fractional shortening and rate-adjusted circumferential shortening velocity were significantly higher and end-systolic wall stress was significantly reduced after transplantation.

Emax (Table 2, Fig. 3). No significant change in Emax or X intercept occurred between groups after dialysis or transplantation (Table 2). In addition, in contrast to fractional shortening and rate-adjusted shortening velocity, in all individuals the difference between sequential studies was minimal. All Emax values were within the range of normal for our laboratory ($\geq$90 mm Hg/cm per $m^{2/3}$), indicating normal contractility.

Ejection phase indexes and loading conditions (Fig. 4 and 5). Five of nine subjects were noted to have abnormal ejection phase indexes of ventricular function (defined as fractional shortening $<28\%$ or rate-adjusted velocity of shortening <0.90) at one or more evaluations. However, when the effect of afterload was examined by considering the end-systolic wall stress to rate-adjusted shortening velocity relation, all data points were within the normal range (27), indicating normal contractility (Fig. 4, upper panel). When the relation of fractional shortening to end-systolic wall stress was examined, three of nine subjects were noted to have abnormally low values while receiving long-term dialysis (Fig. 4, lower panel). The end-systolic wall stress to fractional shortening relation is influenced by both preload

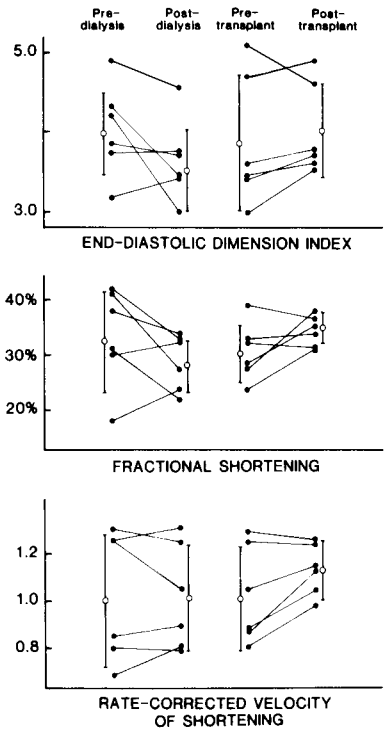


Figure 2. Effect of dialysis and renal transplantation on end-diastolic dimension index, fractional shortening and rate-adjusted shortening velocity in each subject. Although large changes occurred in some individuals, only the mean changes in fractional shortening and rate-adjusted shortening velocity after renal transplantation attained statistical significance.

status and contractility (27), and in the presence of normal contractility (as indicated by both the Emax and end-systolic wall stress to rate-adjusted velocity of shortening values) an abnormally low end-systolic wall stress to fractional shortening relation implies a low preload.

The effect of dialysis or renal transplantation, or both, on left ventricular loading conditions in two subjects is illustrated in Figure 5. In Subject 5, dialysis was associated with a significantly higher afterload (greater end-systolic wall stress) with no change in contractility (the end-systolic wall stress to rate-adjusted shortening velocity relation changed in a fashion parallel to the mean population regression line b_1 to b_2 in Fig. 5, upper panel. Subject 2 had no change in afterload or contractility after dialysis (a_1 to a_2 in Fig. 5, upper panel). Both subjects, however, demonstrated a significant reduction in the end-systolic wall stress to fractional shortening relation (movement orthogonal to the mean regression line a_1 to a_2 and b_1 to b_2 in Fig. 5, lower panel). In the presence of unaltered contractile state, this finding implies significant preload reduction (27). After transplantation, subject 5 had a lower afterload (reduced end-systolic wall stress), no change in contractility (position of the end-systolic wall stress to rate-adjusted velocity of shortening relation with respect to the mean regression line [b_2 to b_3

Table 2. Effect of Dialysis and Renal Transplantation on all Variables in Each Subject

Patient No.	Status	BSA	HCT	BUN	Cr	SBP	DBP	HR	EDD	EDDI	ESD	FS	Vcfc	ESS	Emax	X Int
1	Predialysis	0.51	21	112	6.7	124	68	116	3.0	3.8	2.1	30%	0.85	51	97	1.19
	Postdialysis	0.56	22	89	5.2	102	59	140	3.1	3.8	2.1	32%	0.89	45	93	1.27
2	Predialysis	1.73	22	140	11.2	165	106	93	5.9	4.9	4.1	31%	0.79	98	129	2.17
	Postdialysis	1.68	23	105	13.6	155	99	74	5.4	4.6	4.2	22%	0.78	96	140	2.22
3	Predialysis	1.42	17	91	10.2	115	65	47	4.3	3.8	2.7	37%	1.25	27	115	1.87
	Postdialysis	1.42	23	69	9.3	106	61	67	4.2	3.7	2.8	33%	1.30	24	110	1.78
4	Predialysis	0.63	12	144	6.7	126	85	120	3.6	4.2	2.1	42%	1.30	26	173	1.86
	Postdialysis	0.59	28	67	8.4	116	84	104	2.5	3.0	1.7	32%	1.26	32	174	1.43
	Posttransplant	0.61	37	14	0.4	119	83	93	3.0	3.5	2.0	33%	1.24	30	164	1.65
5	Predialysis	0.93	24	88	6.1	138	78	137	3.1	3.2	1.8	42%	1.24	20	140	1.15
	Postdialysis	0.91	23	80	8.9	188	128	130	3.3	3.4	2.4	27%	1.05	55	152	1.30
	Posttransplant	0.99	39	20	0.8	119	70	100	3.7	3.7	2.3	38%	1.15	29	140	1.44
6	Predialysis	1.07	22	77	5.9	141	101	107	5.5	4.3	4.5	18%	0.68	104	—	—
	Postdialysis	1.07	19	61	5.8	138	83	120	4.6	3.4	3.5	24%	0.80	85	—	—
	Posttransplant	1.26	29	20	1.4	110	58	84	4.3	4.0	3.0	30%	1.03	40	—	—
7	Pretransplant	0.97	24	81	9.8	156	87	80	5.0	5.1	3.4	32%	0.88	70	90	1.76
	Posttransplant	0.97	39	26	0.8	114	53	57	4.5	4.6	3.1	34%	1.05	26	97	1.89
8	Pretransplant	1.41	28	66	10.0	102	61	82	5.3	4.7	3.9	28%	0.86	62	103	2.47
	Posttransplant	1.46	40	22	0.9	117	58	53	5.5	4.9	3.6	35%	1.13	33	96	2.07
9	Pretransplant	0.65	19	75	7.1	104	58	139	3.1	3.6	1.8	39%	1.30	29	127	1.41
	Posttransplant	0.67	42	17	0.2	135	85	105	3.2	3.7	2.0	37%	1.27	35	118	1.35
Mean	Predialysis	1.05	20	109	7.8	135	84	103	4.2	4.0	2.9	33	1.02	54	130	1.6
± SD		± 0.47	± 4	± 29	± 2.3	± 18	± 17	± 31	± 1.2	± 0.6	± 1.1	± 9.1	± 0.27	± 38	± 28	± 0.5
Mean	Postdialysis	1.04	23	79*	8.5	124	86	106	3.9	3.6	2.8	28	1.01	56	131	1.6
± SD		± 0.42	± 3	± 26	± 2.1	± 20	± 27	± 30	± 1.1	± 0.5	± 0.9	± 4.6	± 0.22	± 29	± 31	± 0.4
Mean	Pretransplant	0.93	24	72	8.3	132	84	103	4.0	3.9	2.8	31	1.05	56	129	1.7
± SD		± 0.30	± 4	± 8	± 1.6	± 34	± 25	± 26	± 1.1	± 0.8	± 0.9	± 5.3	± 0.19	± 22	± 34	± 0.5
Mean	Posttransplant	0.99	38	20*	0.8*	119	68	82*	4.0	4.1	2.7	35*	1.15*	29*	123	1.8
± SD		± 0.27	± 5	± 7	± 1.5	± 9	± 14	± 22	± 0.9	± 0.6	± 0.7	± 2.9	± 0.10	± 5.3	± 29	± 0.4

*p 0.05 versus status before intervention. BSA = body surface area (m^2); BUN = blood urea nitrogen (mg/dl); Cr = creatinine (mg/dl); DBP = diastolic blood pressure (mm Hg); EDD = end-diastolic dimension (cm); EDDI = indexed end-diastolic dimension ($cm/m^{2/3}$); Emax = normalized slope of end-systolic pressure-dimension relation (mm Hg/cm per $cm^{2/3}$); ESD = end-systolic dimension (cm); ESS = end-systolic stress (g/cm^2); FS = fractional shortening (%); Hct = hematocrit (%); HR = heart rate (beats/min); SBP = systolic blood pressure (mm Hg); SD = standard deviation; Vcfc = rate-corrected shortening velocity (circ/s per $s^{1/2}$); X Int = intercept of the normalized end-systolic pressure-dimension relation ($cm/cm^{2/3}$).

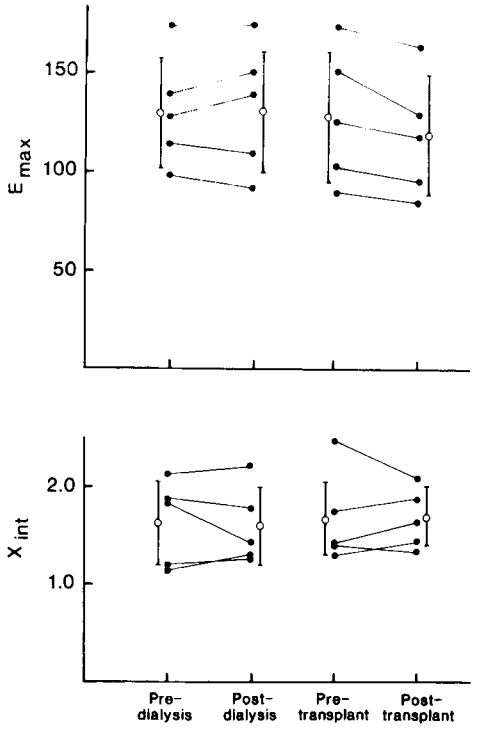


Figure 3. Effect of dialysis and transplantation on Emax and X intercept. Values in all subjects were essentially unchanged by either intervention.

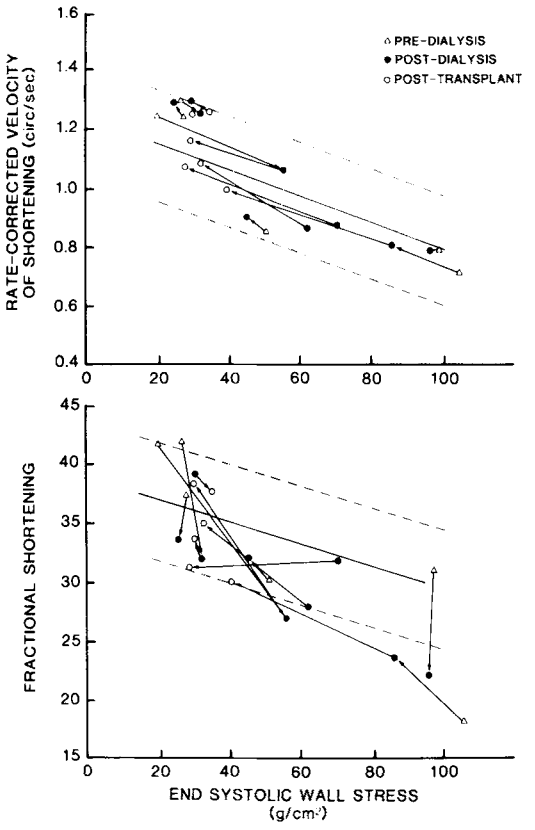


Figure 4. Individual end-systolic stress to rate-adjusted velocity of shortening (**upper panel**) and end-systolic stress to fractional shortening (**lower panel**) data points for all nine subjects. The mean normal regression line and 95% confidence intervals for these indexes in our laboratory are shown. Sequential studies in individual subjects are connected by **arrows.** All end-systolic stress to rate-adjusted shortening velocity values are within the normal range, indicating normal contractility. In contrast, subnormal end-systolic stress to fractional shortening values were found in three subjects after dialysis, indicating reduced preload status. Movement of end-systolic stress to rate-adjusted shortening velocity values in any individual between sequential studies was parallel to the regression line, implying unaltered contractile state.

in Fig. 5, upper panel] was unchanged), and higher preload (higher values of the end-systolic wall stress to fractional shortening relation relative to the mean group regression line in the presence of unaltered contractility [b_2 to b_3 in Fig. 5, lower panel]).

Effects of dialysis and renal transplantation (Fig. 6). When the group data were considered, dialysis was associated with no mean change in afterload or contractility (unaltered end-systolic wall stress and end-systolic wall stress to rate-adjusted velocity of shortening relation) (Fig. 6, upper panel), but a reduction in preload (downward shift of the end-systolic wall stress to fractional shortening relation [Fig. 6, lower panel], with no change in contractility). Transplantation resulted in a significant afterload reduction (lower end-systolic wall stress) and secondary increase in rate-adjusted velocity of shortening and fractional shortening, with no change in contractility (position of the end-systolic wall stress to rate-adjusted velocity of circumferential shortening relation with respect to the group mean regression line unchanged) (Fig. 6, upper panel) or preload (concordance of the end-systolic wall stress to rate-adjusted velocity of shortening and end-systolic wall stress to fractional shortening relation) (Fig. 6). Although the alterations in afterload, preload and ejection phase indexes of ventricular function in the group data followed these patterns, marked individual variation was present for each of these variables. In spite of the large variability in ventricular shortening and loading conditions seen among individuals, the response of contractile state was entirely uniform, showing the same lack of change in each individual with each intervention.

Discussion

Left ventricular contractile state in uremia. In this group of young subjects with end stage renal disease, no abnormalities of left ventricular contractile state were found, nor was there any change in left ventricular contractility after dialysis or renal transplantation. Similar to the findings of previous investigators, when ventricular function is evaluated using the usual ejection phase indexes of fractional shortening or velocity of shortening, most uremic patients

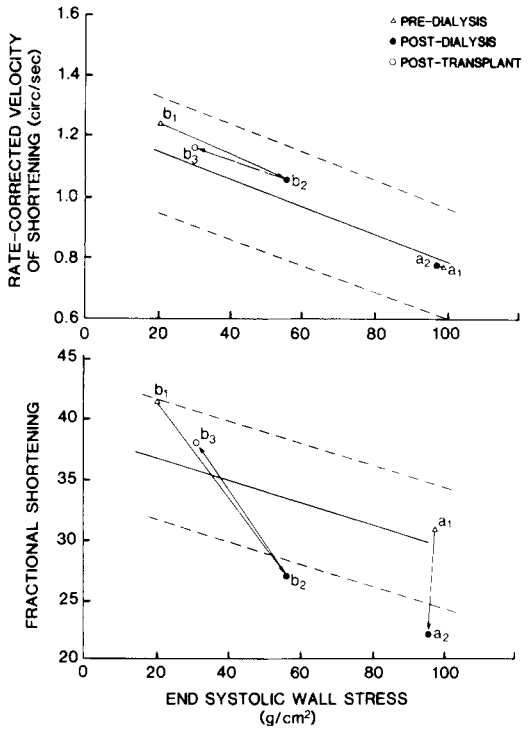


Figure 5. Effect of dialysis or transplantation, or both, on the end-systolic stress to rate-adjusted shortening velocity relation (**upper panel**) and the end-systolic stress to fractional shortening relation (**lower panel**) in two representative subjects. Subject 2 had no change in afterload or contractility (unchanged end-systolic stress to rate-adjusted shortening velocity relation) after dialysis, but a marked reduction in preload (a_1 to a_2 in **lower panel**) was found. After dialysis, Subject 5 had an increase in afterload (higher end-systolic stress) with no change in contractility (distance of the end-systolic stress to rate-adjusted shortening velocity relation from the mean regression line is unchanged [b_1 to b_2 in **upper** panel]). There was an associated reduction in preload, as indicated by the decrease in the end-systolic stress to fractional shortening relation in spite of an unaltered contractile state. After transplantation (b_2 to b_3), the reverse was seen, with lower afterload, higher preload and no change in contractility.

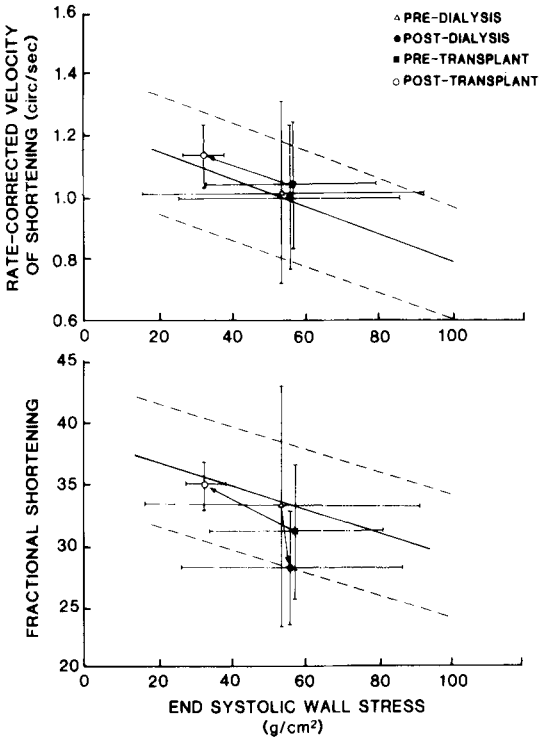


Figure 6. Mean values (± SD) of the relation of end-systolic stress to rate-adjusted shortening velocity (**upper panel**) and fractional shortening (**lower panel**) in the four patient categories (before and after dialysis and transplantation). In general, dialysis was associated with no change in contractility (end-systolic stress to rate-adjusted shortening velocity relation is unaltered) and a decrease in preload (movement of the end-systolic stress to fractional shortening relation away from the mean regression line without altered contractility). In contrast, renal transplantation was associated with a reduced afterload (lower end-systolic stress), no change in contractility (end-systolic stress to rate-adjusted shortening velocity position with respect to the mean regression line is unaltered) and no change in preload (concordance of the end-systolic stress to fractional shortening and end-systolic stress to rate-adjusted shortening velocity relations).

have abnormal values. We were able to demonstrate that in each case, this was not related to abnormal contractility even in the presence of clinical congestive heart failure, but was secondary to reduced preload or excess afterload, or both. Marked changes in ventricular size and ejection phase indexes were seen with dialysis and renal transplantation, with large interindividual variability. In general, dialysis was associated with a reduction in preload status and a resultant decrease in fractional shortening and end-diastolic dimension, with no change in afterload or contractility. Renal transplantation resulted in a reduction of afterload, with increased fractional shortening and velocity of shortening and no change in preload or contractility. Normalization of loading conditions was invariably associated with restoration of normal ejection phase indexes.

The patients included in this study were young and without other potentially confounding factors such as coronary artery disease or long-standing hypertension. This selection bias enables conclusions to be drawn concerning the direct effects of uremia on myocardial contractility without concern that any observed abnormalities may be secondary to these other factors. In fact, normal contractility was found in all phases of therapy, suggesting that any observed abnormalities of contractility in subjects with chronic renal failure are due to additional complications and are not inherent to the uremic state. Likewise, data were intentionally obtained when patients were in relatively steady state conditions to avoid the potential acute effects of electrolyte shifts in the immediate postdialysis period. The marked heterogeneity of the induced changes in afterload and preload that we observed would be anticipated in an ambulatory group of patients with varying degrees of residual renal

function, hypertension and fluid and electrolyte intake. In spite of marked and varying alteration of loading conditions, however, myocardial contractility remained remarkably constant.

Is there a uremic cardiomyopathy? The existence of a specific uremic cardiomyopathy has been controversial (34,35). Previous investigators have noted abnormal ejection fraction (1,2), stroke work index (4,18), velocity of shortening (1,2,5,6,12,13,16,21), systolic time intervals (5,14,16,19,22) and fractional shortening (6,12,15) in uremic patients. Interpretation of these findings is problematic since, as shown in this study, afterload and preload are frequently abnormal in this group and each of these indexes is highly dependent on ventricular loading conditions. In general, left ventricular loading status either has not been assessed or has been assessed with use of inadequate measures. In particular, blood pressure has often been used as a measure of ventricular afterload. However, the extent of myocardial shortening is determined by the force-resisting fiber shortening at end-systole, which is best represented by end-systolic wall stress (27,36). According to the Laplace relation, wall stress is determined by pressure, dimension and wall thickness. In situations associated with large changes in ventricular wall thickness or dimension, blood pressure is a particularly unsuitable measure of afterload. In addition, end-systolic pressure has a variable relation to peak or diastolic pressure, further limiting pressure measurements at these points in the cardiac cycle as measures of afterload. For example, we found a significant decrease in wall stress at end-systole after renal transplantation without a significant change in systolic or diastolic blood pressure.

A potentially confounding variable in this study is the higher hematocrit in some patients after dialysis and renal transplantation. Chronic anemia results in augmentation of ejection phase indexes of ventricular function (37). Although this effect has been ascribed to the altered loading conditions that accompany anemia, recent evidence (38) suggests the presence of a noncatecholamine positive inotropic factor in the serum of patients with chronic anemia. However, in that study (38), subjects with renal failure were not included and the effect of this agent on in vivo contractility was not determined. Although it is possible that in our study, a decrease in contractility due to correction of anemia was counterbalanced by an equal and opposite effect of dialysis or transplantation, or both, this appears unlikely because patients who experienced no change in hematocrit did not demonstrate an increase in contractility.

Methodologic considerations. The potential limitations of the methods used for evaluation of left ventricular mechanics have been previously discussed in detail (27,30). The use of ventricular dimension as a measure of left ventricular volume assumes symmetric left ventricular wall motion and normal chamber configuration, factors confirmed in these subjects by two-dimensional echocardiography. The load-independence of Emax within the physiologic range has been confirmed by a number of investigators (28,30). The method employed here for calculation of Emax relies on a large number of data points generated over a wide range of pressure values, thereby avoiding some of the limitations inherent in calculations based on a more limited number of observations. This method involves the direct determination of Emax, eliminating any assumptions concerning the use of systolic blood pressure or the correct timing of end-systolic blood pressure, and avoiding the use of minimal or end-systolic dimension to estimate the true Emax pressure-dimension values. This contrasts with methods that rely on measurement of the end-systolic pressure-volume relation at the time of aortic valve closure as an estimate of Emax (28–30). Finally, the concordance of two different load-insensitive measures of contractile state (Emax and the end-systolic wall stress to rate-adjusted velocity of shortening relation) that are determined from separate data recordings and rely on independent mechanical properties of the myocardium strongly supports the reliability of these findings.

Role of heart rate. Significant alterations in heart rate at rest were noted in individual subjects during sequential evaluations. Studies on excised strips of myocardium (39), isolated hearts (40) and human subjects (41,42) have indicated that acute tachycardia enhances the contractile state of myocardium. In particular, higher Emax values have been found in conscious dogs during atrial pacing-induced tachycardia (43). For this reason, autonomic reflex bradycardia was prevented during methoxamine infusion by pretreatment with atropine, and calculations were performed using data obtained at stable heart rates. In contrast, it was not possible to avoid differences in heart rate in studies before and after dialysis and before and after transplantation. The influence of chronic alterations in heart rate on myocardial contractility are not known. The absence of changes in Emax in parallel with the changes in heart rate and the concordance of Emax values with end-systolic wall stress to rate-adjusted velocity of shortening values (a rate-adjusted index) suggest that this effect is not large.

Role of altered afterload and contractility. This study illustrates the utility of this methodology for distinguishing among the effects of altered afterload, preload and contractility on ventricular function. Preload in particular has been difficult to compare among patients. Although diastolic pressure, volume and wall stress have been commonly used, end-diastolic fiber length is the true determinant of the Frank-Starling effect. The relation of each of these alternative measures to end-diastolic fiber length is dependent on myocardial compliance and zero pressure diastolic volume. By comparing the end-systolic wall stress to fractional shortening and end-systolic wall stress to rate-adjusted velocity of shortening relations, a functional component is included in the analysis that directly reflects the net effect of altered

diastolic pressure and volume on the degree of myofilament overlap. This permits comparisons between subjects and between observations separated in time in individual subjects where alterations in chamber compliance or zero pressure volume may have occurred.

Clinical significance. In addition to direct myocardial depression from a circulating toxin associated with uremia, chronic renal failure has the potential to cause myocardial dysfunction through chronic hypertension (44), premature atherosclerosis due to abnormal carbohydrate and lipid metabolism (45), cardiomyopathy associated with iron overload (46,47) and volume overload injury due to chronic anemia, hypervolemia and iatrogenic arteriovenous fistulas (48,49). We have purposely studied a group at low risk for these potentially confounding elements to permit evaluation of any intrinsic myocardial depressant factor. Although no evidence of such a factor was found, these patients are clearly at high risk for myocardial injury due to other causes, and any abnormalities of contractility observed in these patients must take these additional adverse influences into consideration. However, abnormal ejection phase indexes of ventricular function in a young group of subjects appear secondary to abnormal loading conditions and respond to therapy that normalizes loading status, potentially avoiding the additional hazards associated with the use of digitalis in these subjects.

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