

# Preload Dependence of New Doppler Techniques Limits Their Utility for Left Ventricular Diastolic Function Assessment in Hemodialysis Patients

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**Abstract.** Left ventricular (LV) hypertrophy leads to diastolic dysfunction. Standard Doppler transmitral and pulmonary vein (PV) flow velocity measurements are preload dependent. New techniques such as mitral annulus velocity by Doppler tissue imaging (DTI) and LV inflow propagation velocity measured from color M-mode have been proposed as relatively preload-independent measurements of diastolic function. These parameters were studied before and after hemodialysis (HD) with ultrafiltration to test their potential advantage for LV diastolic function assessment in HD patients. Ten patients (seven with LV hypertrophy) underwent Doppler echocardiography 1 h before, 1 h after, and 1 d after HD. Early (E) and atrial (A) peak transmitral flow velocities, peak PV systolic (s) and diastolic (d) flow velocities, peak *e* and *a* mitral annulus velocities in DTI, and early diastolic LV flow propagation velocity ( $V_p$ ) were measured. In all patients, the E/A ratio after HD (0.54; 0.37 to 1.02) was lower ( $P < 0.01$ ) than before HD (0.77; 0.60 to 1.34). E decreased ( $P < 0.01$ ), whereas A did not. PV s/d

after HD (2.15; 1.08 to 3.90) was higher ( $P < 0.01$ ) than before HD (1.80; 1.25 to 2.68). Tissue *e/a* after HD (0.40; 0.26 to 0.96) was lower ( $P < 0.01$ ) than before HD (0.56; 0.40 to 1.05). Tissue *e* decreased ( $P < 0.02$ ), whereas *a* did not.  $V_p$  after HD (30 cm/s; 16 to 47 cm/s) was lower ( $P < 0.01$ ) than before HD (45 cm/s; 32 to 60 cm/s). Twenty-four hours after the initial measurements values for E/A (0.59; 0.37 to 1.23), PV s/d (1.85; 1.07 to 3.38), *e/a* (0.41; 0.27 to 1.06), and  $V_p$  (28 cm/s; 23 to 33 cm/s) were similar as those taken 1 h after HD. It is concluded that, even when using the newer Doppler techniques DTI and color M-mode, pseudonormalization, which was due to volume overload before HD, resulted in underestimation of the degree of diastolic dysfunction. Therefore, the advantage of these techniques over conventional parameters for the assessment of LV diastolic function in HD patients is limited. Assessment of LV diastolic function should not be performed shortly before HD, and its time relation to HD is essential.

Intradialytic hypotension is an important complication of hemodialysis (HD), and its pathogenesis is not completely understood. It frequently requires intervention, which limits the efficacy of HD. The incidence is 25% with a range of 15 to 50% (1–3) and increases with age. Hypotension results from a decreased product of stroke volume (SV), heart rate, and systemic vascular resistance. Compensatory mechanisms, such as tachycardia and arterial vasoconstriction, require adequate venous return. Ultrafiltration (UF) withdraws volume from the hemodynamically active “central” circulation, whereas most of the volume overload resides in the interstitial and, to a lesser extent, in the intracellular compartment. The venous system contains an important buffer against hypovolemia (2,4–6). However, if plasma-refilling rate lags behind UF rate, then intravascular volume depletion may exceed the limit of the

buffer capacity, and venous return falls. Maintaining adequate cardiac filling when venous pressure decreases critically depends on the diastolic function of the left ventricle (LV).

LV hypertrophy (LVH) is common in ESRD (7,8). While LV systolic function remains normal (9,10), myocardial relaxation decreases as a result of a slower reuptake of calcium by the sarcoplasmic reticulum, leading to decreased LV filling (11). Myocardial fibrosis, which is more prominent in ESRD than in nonuremic patients with similar LV mass index (LVMI), results in a decreased compliance. Factors in the pathogenesis of myocardial fibrosis include angiotensin II, chronically elevated parathyroid hormone (PTH), endothelin, aldosterone, and increased plasma catecholamines (11).

For assessing LV diastolic function, pulsed Doppler transmitral and pulmonary vein (PV) flow velocities are used. These parameters are known to be preload dependent (12,13). This is a confounding factor in HD patients, in whom filling pressure changes independent of cardiac function, as the volume status is acutely altered by UF. Predialysis overhydration leads to a high preload, which may mask impairment of early diastolic filling. Conversely, HD with UF reduces preload, resulting in decreased peak early filling velocities and a pattern of diastolic dysfunction. The effect of preload changes is crucial and

Received November 14, 2002. Accepted March 23, 2003.

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1046-6673/1407-1858

Journal of the American Society of Nephrology

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DOI: 10.1097/01.ASN.0000072745.94551.FC

therefore must be accounted for in the assessment of LV diastolic function in HD patients.

New Doppler measurements that are relatively preload independent have been proposed (14–19). These could be particularly helpful in the diagnosis of diastolic dysfunction in HD patients. Doppler tissue imaging (DTI) assesses the LV myocardial tissue velocities during diastole. Color M-mode assesses the velocity of the diastolic flow propagation velocity ( $V_p$ ) from the mitral orifice to the apex over time. The aim of the present study was to test the preload dependence of these new echo Doppler parameters in HD patients.

## Materials and Methods

### Patients

Ten HD patients (5 men and 5 women; median age, 54; range, 38 to 80 yr) were included in this study. Median time on HD was 2.5 yr (range, 1 to 7 yr). Eight patients had no history of cardiac disease. One patient had undergone coronary artery bypass graft surgery 7 yr before. One patient had a history of unstable angina pectoris treated successfully by percutaneous transluminal angioplasty with stent placement 2 yr before. None of them had symptomatic ischemic heart disease, significant (>1+) valvular disease, or congestive heart failure. The ethical review committee of our hospital approved the study, and written informed consent was obtained from all patients.

### Hemodialysis

All patients underwent dialysis following a standard dialysis prescription, which had been unchanged for several weeks. Dry weight was considered optimal when patients remained without symptoms of dyspnea, orthopnea, or edema during the interdialytic period. Inferior vena cava (IVC) diameter was measured. Overhydration was defined as an IVC diameter of >11.4 and underhydration as an IVC diameter of <8.0 mm/m<sup>2</sup> (20,21). Hypotension was defined as a drop in systolic BP of >30% or below 100 mmHg.

All dialysis treatments used a Fresenius 4008 H machine, biocompatible membranes (Hemophane or Polysulphone), and bicarbonate-buffered dialysate (Fresenius Medical Care SK-F213). Composition of dialysate was as follows (in mmol/L): Na<sup>+</sup> 138, K<sup>+</sup> 2.00, Ca<sup>2+</sup> 1.75, and HCO<sub>3</sub><sup>-</sup> 32.00. Four patients underwent dialysis twice weekly, the others three times a week.

### Echocardiography

Two-dimensional echocardiography and Doppler studies were performed 1 h before HD with UF and repeated 1 h after the end of HD, assuming the process of plasma refilling to be completed by that time. These measurements were repeated 24 h after the initial echo Doppler in all but one subject.

Echocardiograms were obtained using a General Electric Vingmed System 5 machine equipped with a 3.5-MHz transducer (GE Vingmed, Horton, Norway). The same experienced echocardiographer performed all measurements. LV mass was calculated from Penn convention measurements according to Devereux and Reichek (22). LVMI by height was used for the diagnosis of LVH according to the Framingham Study. LVMI ≥143 g/m for men and ≥102 g/m for women was considered diagnostic of LVH (23,24). SV and fractional shortening (FS) were calculated from measurements in M-mode of end-diastolic and end-systolic diameters to obtain an estimate of LV systolic function.

Transmitral pulsed-wave Doppler velocities were recorded in the apical four-chamber or apical long-axis view. The sample volume was

located at the tips of the mitral valve leaflets. Peak E and A transmitral flow velocities as well as deceleration time of early transmitral flow velocity were measured (Figure 1). Pulsed-wave Doppler velocities of systolic and diastolic forward flow were measured in the right upper PV. With the use of DTI, in which the sample volume was located at the interventricular septal wall at the level of the mitral annulus, the velocities of motion of the mitral annulus were recorded in spectral pulsed mode. Diastolic dysfunction has been defined as  $e < 8$  cm/s (19). Flow  $V_p$  was measured from color M-mode recordings. The M-mode cursor was positioned through the center of the transmitral flow, avoiding boundary regions, and aligned in the direction of the inflow jet. Diastolic dysfunction has been defined as  $V_p < 45$  cm/s (19).

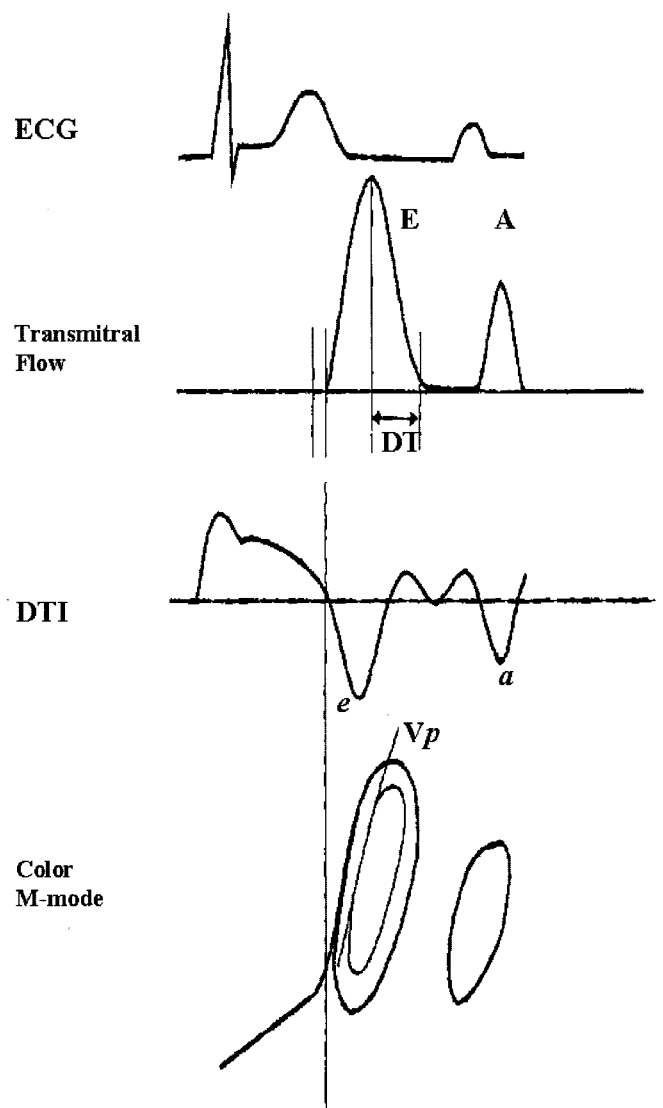


Figure 1. Peak early (E) and atrial (A) transmitral pulsed-wave Doppler velocities and deceleration time (DT) of early transmitral flow velocity. With the use of Doppler tissue imaging (DTI), two distinct signals that are directed away from the LV centroid are obtained during early (e) and late (a) diastole. Flow propagation velocity ( $V_p$ ) is measured from color M-mode recordings as the slope of the first aliasing velocity during early filling from the mitral valve plane into the LV cavity.

Flow and tissue velocities were recorded on videotape, digitized, and transferred to a magneto-optical disk. In an off-line workstation, five consecutive beats were analyzed and mean velocity values were calculated to minimize the measurement variability resulting from respiration.

### Statistical Analyses

The change in each echo Doppler parameter before and after HD was analyzed by the Wilcoxon matched pairs test.  $P < 0.05$  was considered to indicate statistical significance. Data are presented as median values and range.

## Results

Five patients developed hypotension during the dialysis treatment. In these patients, UF was temporarily halted and patients were placed in supine position, but no fluid had to be infused to continue HD. Median UF volume was 2200 ml (1000 to 3781 ml). IVC diameter before was 10.3 mm/m<sup>2</sup> (4.6 to 11.6 mm/m<sup>2</sup>), so there was no excessive overhydration. Median IVC diameter after HD was 9.7 mm/m<sup>2</sup> (4.0 to 11.0 mm/m<sup>2</sup>), and all patients reached dry weight.

Serum calcium corrected for serum albumin was 2.35 mmol/L (2.17 to 2.58 mmol/L) before HD and 2.82 mmol/L (2.60 to 3.10 mmol/L) at the end of HD. PTH was 114 ng/L (20 to 461 ng/L).

LVMI measured before HD was 146 g/m (117 to 307 g/m) for men and 139 g/m (86 to 196 g/m) for women. LVMI measurements after HD were not significantly different (157 g/m, 101 to 217 g/m for men; 136 g/m, 79 to 148 g/m for women). Thus, three of four men and four of five women met criteria for LVH as measured both before and after HD. The other three had LVMI within normal range.

SV (97 ml; 61 to 178 ml) and FS (33%; 24 to 43%) measured before HD indicated reasonable LV systolic function in most patients. SV (64 ml; 39 to 115 ml) and FS (25%; 16 to 45%) were significantly lower ( $P < 0.05$ ) after HD.

Seven patients had trace mitral regurgitation before HD. After HD, five of them had no mitral regurgitation at all, whereas in two patients, mitral regurgitation was unchanged. Five patients had trace to maximally 1+ aortic regurgitation, which did not change after HD.

In all patients, E/A after HD (0.54; 0.37 to 1.02) was significantly lower ( $P < 0.01$ ) than before HD (0.77; 0.60 to 1.34; Figure 2, Table 1). E decreased ( $P < 0.01$ ), whereas A did not. There was no significant change in deceleration time of early transmitral flow velocity. The systolic to diastolic (s/d) ratio of peak PV flow velocity after HD (2.15; 1.08 to 3.90) was significantly higher ( $P < 0.01$ ) than before HD (1.80; 1.25 to 2.68). Tissue *e/a* after HD (0.40; 0.26 to 0.96) was significantly lower ( $P < 0.01$ ) than before HD (0.56; 0.40 to 1.05). Tissue *e* decreased ( $P < 0.02$ ), whereas *a* did not.  $V_p$  after HD (30 cm/s; 16 to 47 cm/s) was significantly lower ( $P < 0.01$ ) than before HD (45 cm/s; 32 to 60 cm/s).

Twenty-four hours after the initial measurements before HD, at the same time as the start of HD the previous day, values for E/A (0.59; 0.37 to 1.23), PV s/d (1.85; 1.07 to 3.38), *e/a* (0.41; 0.27 to 1.06), and  $V_p$  (28 cm/s; 23 to 33 cm/s) did not differ

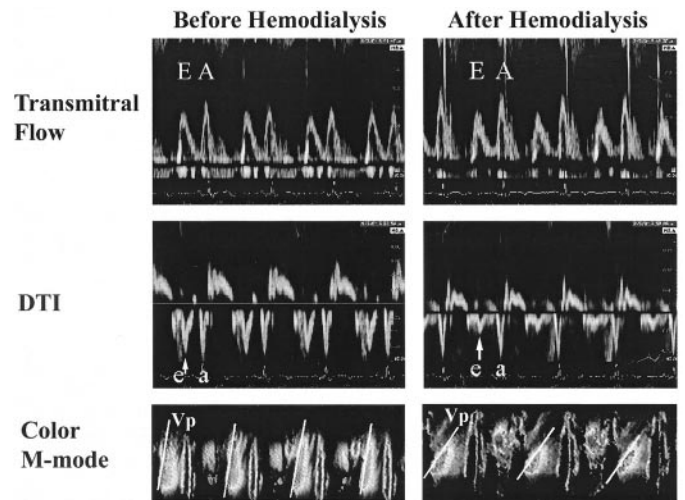


Figure 2. Change in peak transmitral flow velocities (E and A), peak mitral annulus velocities (*e* and *a*), and flow  $V_p$  after hemodialysis.

from those taken 1 h after HD. IVC diameter 24 h later (8.8 mm/m<sup>2</sup>; 4.0 to 11.6 mm/m<sup>2</sup>) was not significantly different from IVC diameter 1 h after HD.

## Discussion

The results of this study are in keeping with a masking effect of predialysis hypervolemia on the impairment of early LV diastolic filling, resulting in pseudonormalization of transmitral blood flow pattern. After HD, in all patients, the E/A ratio was reduced as a result of a significant decrease in peak E velocity. After reaching dry weight, all but one of the patients had E/A ratios consistent with LV diastolic dysfunction. The next day, E/A was not significantly different from E/A 1 h after HD. As the IVC diameter the next day was also not significantly different from the IVC diameter 1 h after HD, it seems that relative overhydration leading to pseudonormalization occurs shortly before the start of HD.

Seven patients had trace mitral regurgitation before HD, which may have augmented pseudonormalization by increasing left atrial pressure. This mild mitral regurgitation might have been caused by increased LV stretch as a result of volume overload, because it was undetectable in five patients after volume withdrawal.

A pattern of preload dependence was also found in PV flow measurements. The preload dependence of conventional transmitral and PV flow measurements is a well-recognized phenomenon, which hampers the assessment of diastolic function in HD patients. Preload is the degree of stretch of the cardiac muscle at the start of LV contraction, which depends on the degree of end-diastolic ventricular filling. Peak transmitral flow is the result of the combined effects of end-systolic left atrial pressure and the LV pressure–volume relationship. This pressure–volume relationship depends on the intrinsic LV characteristics of relaxation and compliance and determines the LV pressure for a certain degree of ventricular filling. A preload-independent measurement of LV diastolic function

Table 1. Echo parameters before and after HD

		Before HD		After HD		P
		Median	Range	Median	Range	
IVC/BSA	mm/m <sup>2</sup>	10.3	4.6–11.6	9.7	4.0–11.0	<0.01
E	cm/s	65	50–91	52	36–75	<0.01
A	cm/s	86	53–119	82	65–120	NS
E/A		0.77	0.60–1.34	0.54	0.37–1.02	<0.01
DT	s	217	130–383	251	166–312	NS
PV s/d		1.80	1.25–2.68	2.15	1.08–3.90	<0.01
e	cm/s	6	4–9	4	3–8	<0.02
a	cm/s	10	5–14	10	4–14	NS
e/a		0.56	0.40–1.05	0.40	0.26–0.96	<0.01
V <sub>p</sub>	cm/s	45	32–60	30	16–47	<0.01

BSA, body surface area; DT, deceleration time of E.

would be expected to reflect LV relaxation and compliance only.

Contrary to expectation, the newer techniques DTI and color M-mode Doppler, which have been proposed as relatively “preload-independent” echo Doppler parameters, exhibited a pattern of preload dependence similar to that displayed by the conventional pulsed-wave Doppler flow velocity measurements. It is possible that these newer techniques are preload independent within certain physiologic limits only.

In DTI, as in transmitral flow measurements, the increase in e/a ratio before HD was due to a significant increase in early diastolic velocities. Nevertheless, median e before HD was already indicative of diastolic dysfunction. Likewise, using color M-mode, V<sub>p</sub> before HD indicated borderline diastolic function. Both Doppler parameters showed a further deterioration after HD, which persisted the next day.

In view of the demonstrated preload dependence, it is important that when measurements of LV diastolic function in HD patients are reported, both the time relation and the volume status are specified. It seems preferable to assess diastolic function in a relatively normovolemic state, at least 1 h after HD.

Alternatively, DTI may reflect the actual diastolic function, which suggests that HD impairs cardiac relaxation and thereby worsens LV diastolic function. This could be caused by the shift in serum ionized calcium concentration during HD. Decreased availability of calcium to the myocardium could impair both myocardial contraction and relaxation. Doppler parameters the next day were not different from those measured 1 h after HD. Therefore, it seems less likely that acute changes related to the shifts in solutes caused the deterioration of diastolic function.

The decrease in SV and FS indicated a deterioration of LV systolic function after HD. Such a change in systolic function is another variable with a potential adverse effect on diastolic function. LV systolic function was previously found to be normal and to remain unchanged after HD (10,25). However, different measures of cardiac pump function have been used, some of which are affected by volume changes, as may have

been the case in our population. So even though myocardial contractility seemed to remain unchanged or even slightly improved in some studies, this effect was limited as a result of the load dependence of commonly used measures of LV systolic function (26,27).

As a result of LV diastolic dysfunction, adequate cardiac filling can be achieved only in these patients at high levels of left atrial filling pressure. However, in these patients, who are dependent on high levels of filling pressure, venous return is reduced by UF during HD. The demonstrated LV diastolic dysfunction therefore could play an important role in the pathogenesis of dialysis-related hypotension.

We conclude that even when using the newer Doppler techniques DTI and color M-mode, pseudonormalization, which was due to volume overload before HD, resulted in underestimation of the degree of diastolic dysfunction. Therefore, the advantage of these techniques over conventional parameters for the assessment of LV diastolic function in HD patients is limited. These parameters can be useful, provided that information on their time relation to the HD process is reported and that they are not used on the day of the dialysis treatment before HD.

## Acknowledgments

This work was presented in part at the American Society of Nephrology/International Society of Nephrology World Congress of Nephrology, San Francisco, California, November 2001, and was awarded Best Abstract at the International Society of Blood Purification Congress, Tokyo, Japan, September 2001. The authors gratefully acknowledge Jan Tuin for graphical assistance.

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