THE DUAL EFFECTS OF HEMODIALYSIS ON CARDIAC FUNCTION
ASSESSED BY PULSED DOPPLER ECHOCARDIOGRAPHY

YASUO KUDOH, M.D., SHINICHIROU SATOH, M.D., AKIHITO TSUCHIDA, M.D.
SHINICHI HIKITA, M.D., YASUKI SASA, M.D.
AND OSAMU IIMURA, M.D.

To assess the effect of hemodialysis on cardiac function, a change of preload due to water removal was considered. In order to keep the preload constant during hemodialysis, extracorporeal ultrafiltration was induced before hemodialysis (step 1), and then hemodialysis without water removal was achieved (step 2). Cardiac performance in 8 patients was evaluated before and at the end of each step using pulsed doppler echocardiography.

Step 1: Ultrafiltration was 1350 ± 410 ml and hematocrit increased significantly. Left ventricular end-diastolic dimension (LVDd) decreased from 40.3 ± 4.2 (mean ± standard deviation) mm to 36.1 ± 4.6 mm (p < 0.005) and aortic peak flow velocity (PFV) also decreased from 59.9 ± 16.0 cm/s to 49.0 ± 11.0 cm/s (p < 0.005).

Step 2: In contrast, after hemodialysis without water removal, the mean velocity of circumferential fiber shortening (mVcf) increased from 1.36 ± 0.26 circ/s to 1.86 ± 0.36 circ/s (p < 0.005). PFV and average acceleration (Aa) increased from 49.0 ± 11.0 cm/s to 63.8 ± 11.4 cm/s (p = 0.001) and from 750 ± 220 cm/s/s to 1270 ± 280 cm/s/s (p < 0.001), respectively. During this step, serum potassium and osmolality decreased significantly.

In conclusion, hemodialysis improves cardiac function under constant preload condition and this is due to the direct effects of hemodialysis by the correction of electrolytes and osmolar components such as uremic toxin.

It has been noted that most patients with chronic hemodialysis die of cardio-vascular complications1,2 and the uremic cardiomyopathy or the cardiac performance during hemodialysis has now been high-lighted3 Although the effects of hemodialysis on cardiac function have been evaluated invasively4,5 and recently non-invasively6–15 the results are discordant. One reason for the conflicting results is the different effects on cardiac function of volume and individual metabolic changes during hemodialysis. Therefore, it is necessary to distinguish between the direct metabolic effect of hemodialysis on cardiac function and the influence of preload reduction. The method used to evaluate cardiac function is important when assessing hemodialysis effect on cardiac function. Since most cardiac contractility indices are influenced by loading conditions, any single assessment may not be truly representative of the left ventricular contraction.

In order to keep the preload constant during hemodialysis, extra-corporeal ultrafiltration method (ECUM) was induced before hemodialysis and thereafter hemodialysis was carried out

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The Second Department of Internal Medicine, Sapporo Medical College, Sapporo, Japan
Mailing address: Yasuo Kudoh, M.D., The Second Department of Internal Medicine, Sapporo Medical College, S-1 W-16, Chuo-ku, Sapporo 060, Japan

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without water removal in this study. Doppler echocardiography was used to assess entire left ventricular function, in addition to conventional M-mode and two-dimensional (2D) echocardiography.

MATERIALS AND METHODS

Eight patients (six males and two females), aged 22-67 years, were entered in this study. All patients were undergoing regular hemodialysis treatment twice or three times a week at the Hemodialysis Unit of the Sapporo Medical College. Four patients had diabetes mellitus, three glomerulonephritis, and one chronic pyelonephritis. No patient was taking digitalis or beta-blockers.

Study protocol

Patients were weighed and needles for dialysis were inserted through antecubital arteriovenous fistula.

Step 1:

Extracorporeal ultrafiltration method (ECUM) was performed using 1.0-1.5 m² hollow fiber dialyzer and a variable degree of positive pressure for 1-2 hours. The mean rate of ultrafiltration (1000 ml/hr) was directly determined by collecting the ultrafiltrate in a measuring cylinder. The transmembrane pressure during ultrafiltration was about 200 mmHg.

Step 2:

Following ECUM, hemodialysis without water removal was performed for 3-4 hours, which enabled the preload to be kept constant. The dialysate was Kindaly-3 (Fuso Corporation) which was composed as Na 132 mEq/L, K 2.0 mEq/L, Ca 3.5 mEq/L, Cl 104 mEq/L and acetate 35 mEq/L, or Kindaly-AF1 (Fuso Corporation) which was composed as Na 135 mEq/L, K 2.5 mEq/L, Ca 3.5 mEq/L, Cl 106.5 mEq/L, acetate 8 mEq/L and bicarbonate 30 mEq/L. The actual osmolality values of these dialysates were 295 ± 2 mosm/L and 284 ± 3 mosm/L, respectively. The dialysate flow was 500 ml/min. The patients were weighed again after hemodialysis.

Heparinized blood samples were taken from the arterial line before and at the end of each step and the plasma sodium and potassium, hematocrit and osmolality were determined. Electrolyte determinations were analyzed by autoanalyzer (NOVA I, AHS/Japan Corporation), and plasma osmolality was determined by means of the freezing-point method (Advanced
DigiMatic Osmometer, Advanced Instruments Inc). Hematocrit was determined by centrifuging capillary tube. Hemodynamic parameters such as supine blood pressure, heart rate and echocardiogram were also obtained before and at the end of each step.

Echocardiographic technique

Echocardiographic studies were performed utilizing pulsed doppler velocimeter interfaced with a electronic sector scanner to produce M-mode and real time 2D echocardiographic images as well as blood flow velocity recordings (SSH-65A, Toshiba Corporation). 2D echocardiograms were obtained using standard parasternal long- and short-axis views and apical 2- and 4-chamber views. M-mode records were obtained at the level of chordal tendon between the mitral valve and papillary muscle to evaluate left ventricular function (Fig. 1).

Ascending aortic blood flow was studied using 2.5 MHz transducer (PSD-25A, Toshiba Corporation) positioned in the suprasternal notch. Sample volume depth was adjusted until optimal flow pattern was obtained. The flow signal used to determine the ascending aortic flow indices was the flow signal from the sample volume depth that produced the greatest maximum blood flow velocity. The maximum velocity was identified by listening to the audible signal from the Doppler velocimeter and noting the peak velocity from the tracing visualized on the oscilloscope screen. Special attention was given to keep the angle of the ultrasound beam within 20 degrees of the long axis of blood flow. Sample depth and position in the aortic arch remained constant during study. Doppler aortic flow was recorded at held expiration and a series of Doppler tracings were averaged. Hard-copy recordings of the aortic flow were obtained using line scan recorder (LSR-20B, Toshiba Corporation) at a paper speed of 50 or 100 mm/s (Fig. 2).

The left ventricular end-diastolic dimension (LVDd) was measured at the peak of the R wave of the electrocardiogram (ECG) and left ventricular end-systolic dimension (LVDs) was measured at the point of maximum anterior excursion of the posterior left ventricular endocardial echoes. The fractional shortening (%FS) was calculated as (LVDd - LVDs)/LVDd and mean velocity of circumferential fiber shortening (mVcf) was calculated as %FS/ET, where ET is ejection time.

Peak aortic flow velocity (PFV) was measured at the midpoint of the Doppler flow spectrum at the point of maximum blood flow velocity. Ejection time (ET) was measured as the time from the onset to the end of the systolic flow velocity signal. Acceleration time (AT) was measured from the onset of ejection to the point of peak flow velocity. Average acceleration (Aa) of blood flow was calculated as PFV/AT (Fig. 2).

Statistics
In order to compare the values from each step after the sequential processing, a two-way layout analysis of variance (ANOVA) was applied and Tukey's method was used for multiple comparison. P-values of more than 0.05 (bilateral t-distribution test) was considered to be significant.

RESULTS
The results are summarized in Table 1

**Step 1:**
Ultrafiltration was $1350 \pm 410$ (mean \pm standard deviation) ml. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) and heart rate (HR) remained constant during this step. Although LVDd decreased significantly from $40.3 \pm 4.2$ mm to $36.1 \pm 4.6$ mm ($p < 0.005$), LVDs, %FS and mVcf were not significantly changed.

PFV decreased from $59.9 \pm 16.0$ cm/s to $49.0 \pm 11.0$ cm/s ($p < 0.005$). However, Aa was not significantly different. Because of the water removal, hematocrit levels increased significantly from $23.2 \pm 3.4\%$ to $26.2 \pm 4.1\%$ ($p < 0.005$). Serum Na and K, and plasma osmolality were not influenced by this maneuver.

**Step 2:**
Water balance was $50 \pm 320$ ml during this step, which means that the volume remained constant. SBP, DBP and HR were not changed by this procedure. However, if SBP were compared to the control value, the difference was significant ($p < 0.05$). It is interesting to see that the echocardiographic changes after this step might be completely opposite to that after step 1. LVDd was not changed. However, LVDs decreased to $20.7 \pm 4.3$ mm compared to the control value, of $24.7 \pm 6.4$ mm. Both %FS and mVcf increased significantly from $35.9 \pm 9.8\%$.
to 46.4 ± 11.2%, and from 1.36 ± 0.26 circ/s to 1.86 ± 0.36 circ/s, respectively. These changes were significant, even when compared to the control values. PFV increased from 49.0 ± 11.0 cm/s to 63.8 ± 11.4 cm/s and Aa also increased from 750 ± 220 cm/s/s to 1270 ± 280 cm/s/s (p < 0.001). This increase in Aa was significant, even when compared to the control value, of 900 ± 260 cm/s/s (Fig. 3). Although serum Na concentration remained constant, serum K concentration decreased significantly from 4.19 ± 0.87 mEq/L to 3.50 ± 0.49 mEq/L after this step (p < 0.001). Plasma osmolality decreased significantly to 289 ± 11 mOsm/L, when compared to the control value, of 303 ± 16 mOsm/L (p < 0.025).

**DISCUSSION**

Hemodynamic studies in chronic hemodialysis patients have been performed vigorously during the past two decades. However, the results were conflicting. Some investigators reported an increase in cardiac output during hemodialysis when assessed by an invasive method, while others reported a decrease of cardiac index during hemodialysis. Some investigators found an increase in the pre-ejection period during hemodialysis when assessed by systolic time interval, but others, including the same group recently, did not. Some investigators noted the increase of mVcf during hemodialysis by the echocardiographic assessment, but others did not. Some investigators reported either an unchanged or an increased ejection fraction during hemodialysis, but others also reported a decrease of ejection fraction during hemodialysis. One reason why the results were so conflicting is the different effect on cardiac function of volume and metabolic changes during hemodialysis among individuals. In order to evaluate the direct effect of hemodialysis on cardiac function, volume change should be considered separately. In addition, most parameters used to estimate cardiac contractility in previous reports are influenced by loading conditions.

In this study, ultrafiltration was performed before hemodialysis. Thereafter, hemodialysis without water removal was achieved in order to assess the metabolic effects of hemodialysis on the cardiac performance independently from the preload reduction. In addition, doppler echo-
cardiography was applied to evaluate the entire left ventricular function. It added some extra-information about the cardiac contractility to the conventional M-mode or 2D echocardiography.

After step 1 (ultrafiltration only), LVDd decreased and hematocrit increased significantly by volume removal. PFV also decreased significantly. This mechanism may be due to two causes. First, the preload reduction may have reduced the stroke volume itself. Because LVDs, %FS, mVcf and Aa were not significantly changed after this step, reduction of PFV may be a reflection of the Frank-Starling effect. Second, the rise in hematocrit may increase the viscosity, which is the flow resistance according to Poiseuille's low.

In contrast, the change in cardiac performance after step 2 (hemodialysis without water removal) is contrary to that seen after step 1; namely, LVDd was not significantly changed, while LVDs decreased significantly. It has been suggested that end-systolic volume (ESD) is an index of contractility independent of the preload.\(^\text{18,19}\) This is especially true when changes of mVcf with ESD is taken into account. If ESD decreases and mVcf increases, then the contractility is considered to have increased.\(^\text{15}\) In our study, %FS, mVcf and Aa increased significantly after step 2. Therefore, it seems likely that the contractility also, increased during this step.

Although mVcf is relatively independent of the preload change, it is influenced by the afterload and heart rate.\(^\text{20-22}\) In our study, diastolic blood pressure and heart rate did not change, however, systolic blood pressure decreased slightly when compared to the control value. So, afterload reduction partly increase mVcf. In order to assess the change in cardiac function during this step, doppler echocardiographic parameters were adopted.

Although PFV and systolic velocity integral (SVI) have been used as indices of systemic vascular resistance or stroke volume.\(^\text{23}\) Aa and peak acceleration (Pa) are far more sensitive for the evaluation of the inotropic state.\(^\text{24}\) Aa might be an index of cardiac function such as max LV dp/dt theoretically.\(^\text{25}\) It was reported that Aa decreased in patients with cardiomyopathy.\(^\text{26}\) and Pa decreased in patients with myocardial infarction.\(^\text{27}\) Pa increased by exercise and decreased by aging.\(^\text{29}\) Reproducibility of doppler aortic blood flow measurements (intraobserver, inter-observer and day-to-day variability) was confirmed recently in normal subjects.\(^\text{30}\) In our study, Aa increased significantly after step 2. In addition, the increase of %FS and mVcf indicates that hemodialysis improved cardiac contractility under constant preload condition.

The mechanisms of cardiac contractile state improvements during hemodialysis can be summarized as follows: 1) osmolality improvement. It has been reported that uremic toxin depresses cardiac contractility,\(^\text{31}\) therefore osmolality improvement observed in our study could be one of the mechanisms to increase the contractile state. Actually, blood urea nitrogen (BUN) level decreased from 66.4 ± 25 mg/dl to 25.5 ± 13.5 mg/dl in these patients. 2) Electrolyte correction. Serum K decreased significantly after step 2. It is most probable that serum Ca is corrected during this process, because the concentration of Ca was 3.5 mEq/L in our dialysis fluid.\(^\text{32}\) 3) Blood pH correction. Because catecholamine is not effective under metabolic acidosis,\(^\text{33}\) blood pH correction could be one factor to improve the cardiac contractile state. 4) It was reported that the reflex increase in sympathetic tone as a consequence of the reduced stroke volume could have caused the increase in contractility.\(^\text{3}\) However, this hypothesis was not proven by this study, because water removal solely did not cause the increase in contractility and, hemodialysis without volume reduction improved the contractile state. 5) It is well-known that acetate is a strong vasodilator and can affects hemodynamics.\(^\text{34}\) However, in our study blood pressure was not significantly changed and even if bicarbonate had been used as a buffer, the results were similar. Therefore, it is unlikely that acetate plays a role in terms of hemodialysis effects on cardiac function at least in our study.

In conclusion, there are two different mechanisms which influence cardiac performance during regular hemodialysis treatment. One is hemodynamic effect, namely preload reduction, and the other is metabolic effect. These two factors have opposing effects on cardiac state. Overall cardiac function during hemodialysis is determined by the weights of these two factors.

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