Higher ultrafiltration rate is associated with right ventricular mechanical dispersion

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Abstract

Objective: Ultrafiltration rate is one of the major determinants of adverse outcomes in patients undergoing hemodialysis (HD) therapy. Previous studies have focused on the impact of HD on right ventricular (RV) peak strain values. However, the influence of HD on the temporal characteristics of deformation has not been reported yet. The aim of the present study was to evaluate the impact of high ultrafiltration rate (HUR) on RV mechanical dyssynchrony.

Methods: Echocardiographic images focused on the RV and left ventricle (LV) were obtained from 60 patients (49.2±17.3 years, 22 female) before and after HD. Patients were divided into two groups according to ultrafiltration rate. Changes in echocardiographic parameters with HD were examined. Two-dimensional speckle-tracking strain analysis was used to assess deformation. Mechanical dispersion was measured as the standard deviation of time to peak longitudinal strain of six segments for RV and 18 segments for LV.

Results: The average ultrafiltrated volume and ultrafiltration rate were 3000.1±1007.9 mL and 11.4±2.9 mL/kg/h, respectively. Global longitudinal strain (GLS) of the RV and LV decreased after HD in both groups. A significant difference was observed in RV mechanical dispersion with HD for patients in the high ultrafiltration group. A mild statistically insignificant increase in LV mechanical dispersion was also observed after HD.

Conclusion: HUR has a substantial impact on LV and RV GLS and RV dyssynchrony. Ultrafiltration rates and volumes should be kept as low as possible to achieve hemodynamic stability and tolerability. *(Anatol J Cardiol 2019; 21: 206-13)*

Keywords: dispersion, mechanical, right, speckle, tracking, ventricle

Introduction

Patients undergoing hemodialysis (HD) therapy have high cardiovascular mortality rate due to accompanying coronary artery disease, ventricular hypertrophy, myocardial fibrosis, and rapid changes in electrolyte, volume, and acid–base status (1). One of the factors that affect outcome in this population is ultrafiltration rate. Potential ultrafiltration rate-related ischemia and cardiac stress precipitated by high volume depletion can impair cardiac functions and result in myocardial stunning (2, 3). Recurrent cardiac injury due to rapid ultrafiltration causes ventricular remodeling and leads to heart failure and arrhythmias (4, 5). Current data support that a mean ultrafiltration rate of >13 mL/kg/h is associated with higher mortality rates in the long term (6-11). The acute effect of rapid ultrafiltration on the cardiac functions has been investigated in some studies (12); however, there is still a lack of data about the exact relationship between acute rapid ultrafiltration and cardiac functions. All previous studies have been limited into studying the impact of HD on peak strain values, and that the potential influence of HD on the temporal characteristics of deformation and especially mechanical dispersion has not been studied until now. Mechanical dispersion is a parameter that can be easily achieved by two-dimensional (2D) speckle-tracking deformation analysis and has been shown to be related with the outcomes of patients with various types of cardiomyopathies (13-21). As rapid volume change can affect cardiac wall stress and perfusion, we aimed to evaluate the impact of high ultrafiltration rate and volume on right ventricle (RV) and left ventricle (LV) mechanical dyssynchrony.

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Methods

Study population

Patients were recruited from the hemodialysis unit of the Nephrology Department, Gazi University. Inclusion criteria were the following: (1) >18 years old, (2) sinus rhythm at the time of assessment, and (3) receiving systemic bicarbonate HD at least two times a week for at least 6 months. Exclusion criteria were as follows: (1) systolic heart failure or significant valvular pathology, (2) pericardial disease, (3) atrial fibrillation, and (4) acute myocardial ischemia and pulmonary embolism. The study was approved by the Local Ethics Committee. Informed consent was obtained from the patients.

Study protocol

A time interval of 72 h between HD sessions was allotted before the acquisition of echocardiographic images. Dry weight is targeted for each patient during HD session. Weight, heart rate, and blood pressure were measured before and after HD. The ultrafiltrated volume and ultrafiltration rate were recorded. Patients were separated into two groups based on a cut-off value of 13 mL/kg/h for ultrafiltration rate [high ultrafiltration rate (HUR)/acceptable ultrafiltration rate (AUR)].

Echocardiography, strain, and mechanical dispersion analysis

All image acquisitions and echocardiographic examination including strain analysis were performed by an experienced sonographer (S.U.) using a GE Vivid 7 Dimension ultrasonography machine (GE Vingmed Ultrasound, Horten, Norway) equipped with a 3.5 MHz transducer, immediately before and after HD. Echocardiographic examinations were performed in the HD unit. Electrocardiogram and respiration of the patients were monitored. Three cardiac cycle loops were recorded for strain analysis at the end of expiration. The images were analyzed by a vendor-specific software (EchoPAC BT13; GE Vingmed Ultrasound, Horten, Norway). The recommendations of the recent guidelines were followed during echocardiographic analysis (22).

Apical 4-, 2-, and 3-chamber views focused on the LV and apical 4-chamber view focused on the RV were acquired with high frame rate (>60 Hz) for 2D speckle-tracking strain analysis. To define the region of interest on the RV myocardium, the endocardial surface was identified by manually placing at least 15 markings, starting from the lateral annulus and ending at the septal annulus of the tricuspid valve; for LV, the same approach was performed by starting from the septal annulus and ending at the lateral annulus of the mitral valve. End-diastole was indicated by the peak of the R-wave on the electrocardiogram. Global (G) and segmental (S) longitudinal strain (LS) were measured from all six segments of the RV. LV global longitudinal strain (GLS) was derived from the average peak systolic longitudinal strain value of the three apical views. An 18-segment model (three segments per wall) was used to obtain SLS values from the LV according to the recommendations for segmental function analysis. Mechanical dispersion was measured as the standard deviation (SD) of time to peak longitudinal strain of 18 LV segments and 6 RV segments (Fig. 1). The interobserver variability of LV mechanical dispersion measurements was evaluated using intraclass correlation coefficients (ICCs).

Statistical analysis

Continuous variables are presented as mean±SD or median with interquartile range. Categorical data are presented as percentages or frequencies. Kolmogorov–Smirnov test was used to check the normal distribution of continuous variables. Paired t-test and Wilcoxon test were used to compare parametric and non-parametric continuous variables, respectively, before and after HD. Differences between independent groups were compared by using t-test. Categorical variables were compared by chi-square (χ^2) test. Multiple linear regression model including age, ultrafiltration volume, ultrafiltration rate >13 mL/kg/h, RV GLS, and other variables with a univariate relationship (p<0.20) by block entry option was used to evaluate the relationship with RV mechanical dispersion. For assessment of test–re-test, interobserver variability ICCs (two-way mixed model, absolute agreement between single measurements) were used. ICC was interpreted as follows: excellent, ICC≥0.80; good, 0.70≤ICC<0.80; moderate, 0.60≤ICC<0.70; and poor, ICC<0.60. A two-tailed P-value of <0.05 was considered as statistically significant. All data were analyzed using SPSS v23.0 (IBM Corp., Armonk, NY, USA).

Results

Sixty-five patients were included in the final analysis for the assessment of mechanical dispersion of the LV and RV. Twenty-five patients were excluded from the analysis due to bad image quality or newly diagnosed LV pathologies. The mean age of the patients was 49.2±17.3 years. The study included 22 female patients. Table 1 represents the baseline characteristics of participants. The HUR

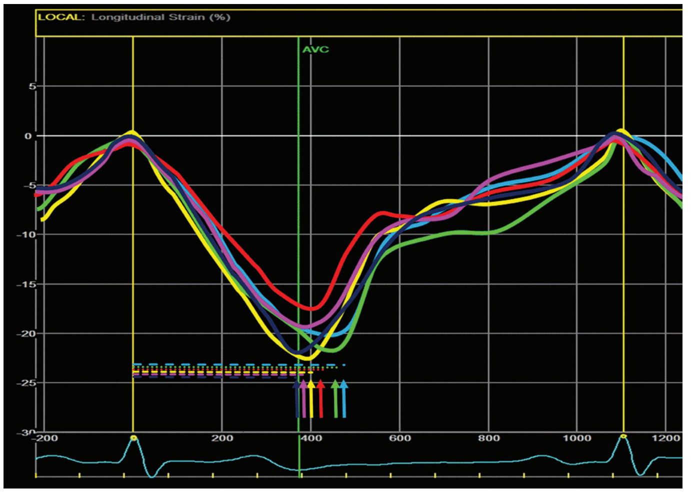

Figure 1. An example of two-dimensional strain curves of the right ventricle for analysis of mechanical dispersion. The arrows represent the time from electrocardiographic onset R to peak segmental longitudinal strain. Mechanical dispersion is assessed by the standard deviation of the six segments coded by colors

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Table 1. Baseline characteristics of the participants

Parameters	Mean/frequency		*P*
	Group HUR (n=23)	Group AUR (n=42)	
Age (year)*	46.1±16.7	48.8±17	0.544
Gender (male) (%)$^{\Omega}$	13 (56.5%)	30 (71.4%)	0.224
BMI (kg/m^2)*	23.3±3.8	22.5±4.3	0.431
Duration of HD (month)*	81.1±50.2	70.8±62.9	0.471
Ultrafiltrated volume (mL)*	3628.3±913.6	2675±900	<0.001
Ultrafiltration rate (mL/kg/h)*	14.6±1.2	9.6±1.9	<0.001
Hypertension$^{\Omega}$	8 (34.8%)	17 (40.5%)	0.651
Diabetes mellitus$^{\Omega}$	5 (21.7%)	10 (23.8%)	0.849
Glomerulonephritis$^{\Omega}$	4 (17.4%)	7 (16.7%)	0.940
Other (polycystic kidney disease, amyloidosis, nephrolithiasis, vesicoureteral reflux, pyelonephritis, autoimmune diseases, and toxic nephropathy)$^{\Omega}$	3 (13%)	5 (11.9%)	0.893
Primary unknown end-stage kidney disease$^{\Omega}$	3 (13%)	4 (9.5%)	0.661

*t-test was used.
$^{\Omega}$Chi-square test was used.
AUR - acceptable ultrafiltration rate; BMI - body mass index; HD - hemodialysis; HUR - high ultrafiltration rate

Table 2. Vital clinical parameters before and after hemodialysis

Parameters	Group HUR (n=23)		*P*	Group AUR (n=42)		*P*
	Before HD	After HD		Before HD	After HD	
SBP (mm Hg)*	115.7±19.7	92±21.7	<0.001	122.1±20.7	104.6±19.5	<0.001
DBP (mm Hg)*	70.1±13.9	56.1±13.7	<0.001	74.2±12	62.3±11.5	<0.001
Heart rate (bpm)*	75.5±10	87.8±14.9	<0.001	77±11.8	81.1±13.6	0.115
Weight (kg)*	65.7±14.5	62.2±13.8	<0.001	66.5±13.1	63.7±12.9	<0.001

*Paired t-test was used.
AUR - acceptable ultrafiltration rate; DBP - diastolic blood pressure; HD - hemodialysis; HUR - high ultrafiltration rate; SBP - systolic blood pressure

group consisted of 23 patients. Systolic and diastolic blood pressures decreased after HD, whereas heart rate increased. Table 2 shows the comparison of clinical parameters before and after HD for both groups.

Conventional echocardiography

Table 3 and 4 list the conventional echocardiographic parameters for RV and LV, respectively. Notable reductions were observed in dimensions, areas, and volumes of both ventricles and atria. LV EF, RV fractional area change (FAC) did not show any significant change between pre- and post-HD examinations for the AUR group, whereas a significant reduction in these parameters was observed in the HUR group.

Strain and mechanical dispersion measurements

LV GLS, RV GLS, and RV free wall LS significantly decreased after HD (Table 5). Decrease was higher in the HUR group. RV mechanical dispersion significantly increased after HD for the HUR group. A significant difference was also observed in RV mechanical dispersion between the HUR and AUR groups after HD. A mild statistically insignificant increase in LV mechanical dispersion was also observed after HD. Table 5 represents the deformation imaging findings for both groups. For linear regression analyses, with age, ultrafiltration volume, ultrafiltration rate >13 mL/kg/h, relative change in systolic blood pressure, and RV GLS, only having higher ultrafiltration rate (>13 mL/kg/h) (r=0.721, p=0.001) and ultrafiltration volume (r=0.654, p=0.004) were significantly associated with RV mechanical dispersion.

Interobserver reproducibility

Analysis of the interobserver variability of RV and LV mechanical dispersion showed good reproducibility [ICC: 0.790, 95% confidence interval (CI): 0.680–0.888 and ICC: 0.800, 95% CI: 0.700–0.878, respectively].

Table 3. Conventional echocardiographic measurements of the right ventricle before and after hemodialysis

Parameters	Group HUR (n=23)			Group AUR (n=42)		
	Before HD	After HD	*P*	Before HD	After HD	*P*
2D biplane measurements of the right ventricle						
RV basal diameter (cm)*	3.3±0.6	2.5±0.5	<0.001	3.2±0.6	2.8±0.5	<0.001
RV midcavity diameter (cm)*	2.1±0.4	1.7±0.4	<0.001	2.1±0.5	1.7±0.4	<0.001
RV longitudinal diameter (cm)*	6.3±0.7	5.7±0.7	<0.001	6.6±0.8	5.8±0.8	<0.001
RV diastolic area (cm^2)*	13.7±3.1	9.9±2.1	<0.001	13.6±3.1	11.6±3.1	<0.001
RV end-systolic area (cm^2)*	7.2±1.7	5.4±1.9	<0.001	7±2.1	6.2±1.9	0.032
RV FAC (%)*	48.9±9.4	46.4±9.7	0.351	46.9±10	46.8±9	0.857
TAPSE (cm)*	2±0.3	1.6±0.4	<0.001	2.2±0.4	1.7±0.3	<0.001
IVC (cm)*	3.0±0.7	1.5±0.4	<0.001	2.8±0.6	1.8±0.5	<0.001
Doppler measurements of the right ventricle						
E (cm/s)*	110±29	53±16	<0.001	101±25	55±14	<0.001
A (cm/s)*	79±19	61±21	0.013	77±24	51±16	<0.001
E/A*	1.5±0.4	1.0±0.4	<0.001	1.4±2	1.0±0.3	<0.001
Deceleration time (ms)*	199.4±80.1	263.1±85.5	0.002	230.8±77	236.8±93.8	0.709
sPAP*	45.4±16.8	22±12.7	<0.001	45.1±17.1	30.9±11.9	<0.001
Tissue Doppler measurements of the right ventricle						
$E'_{lateral}$ (cm/s)*	14.2±4.0	9.7±3.5	<0.001	13.6±3.52	10.1±3.07	<0.001
$A'_{lateral}$ (cm/s)*	16.9±3.9	13.8±4.77	0.001	16.7±4.66	15.2±5.0	0.071
$S'_{lateral}$ (cm/s)*	15±3.0	12.4±3.0	<0.001	14.9±2.86	12.2±3.0	<0.001
$E/E'_{lateral}$*	5.7±2.4	5.8±2.51	0.964	5.3±2.38	5.4±1.92	0.826

*Paired t-test was used.
AUR - acceptable ultrafiltration rate; FAC - fractional area change; HD - hemodialysis; HUR - high ultrafiltration rate; IVC - inferior vena cava; RV - right ventricle; sPAP - systolic pulmonary artery pressure; TAPSE - tricuspid annular plane systolic excursion

Discussion

In the present study, we investigated the impact of ultrafiltration rate on mechanical dyssynchrony of the RV and LV. The main findings were as follows: (1) higher ultrafiltration rates are associated with increased RV mechanical dispersion and (2) LV synchrony did not show difference between the HUR and AUR groups.

Selection of study population

In the present study, we investigated patients with end-stage kidney disease but without significant cardiac diseases, except LV hypertrophy. We had a chance to assess higher volume changes and rates by having the possible longest duration between HD sessions. Systolic and diastolic blood pressures and, accordingly, afterload were decreased after HD in both groups as expected due to fluid loss.

Impact of rapid ultrafiltration on echocardiographic parameters

Transthoracic echocardiography is the first choice for evaluating cardiac function in daily practice because it is a rapid, non-invasive, and repeatable method. Moreover, deformation imaging provides better understanding and evaluation of cardiac mechanics.

Volume status can substantially affect systolic and diastolic functions, indicating that echocardiographic measurements should be interpreted with caution (22). In our study, dimensions, areas, and volumes of cardiac chambers significantly reduced after HD in both groups. There was no significant change observed for RV FAC and LV EF, which are relative measurements of volume changes.

2D speckle-tracking is a method that has been developed for the functional assessment of the LV (23). However, in recent years, its use has been expanded to the RV (24, 25). In the present study, we found a significant reduction in LV GLS, RV GLS, and RV FW LS. The changes were higher for the HUR group. Strain is a load-dependent echocardiographic parameter; additionally, HUR can cause myocardial stunning and higher strain reduction.

Impact of rapid ultrafiltration on mechanical synchrony

Prediction of serious arrhythmias is still challenging despite previous studies mostly focusing on electrical disturbances, such as QT dispersion and heart rate variability (26-33). Unfortunately, outcomes are unsatisfactory and did not change our practice in

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Table 4. Conventional echocardiographic measurements of the left ventricle before and after hemodialysis

Parameters	Group HUR (n=23)			Group AUR (n=42)		
	Before HD	After HD	*P*	Before HD	After HD	*P*
2D biplane measurements of the left ventricle						
LV end-diastolic diameter (cm)*	4.1±0.5	3.7±0.6	0.001	4.4±0.5	4±0.9	0.001
LV end-diastolic volume (mL)*	80.2±28.1	60.1±22.8	<0.001	88.3±30.1	67.5±27.1	<0.001
LV end-diastolic volume index (mL/kg)*	47.8±13.9	36±12.44	<0.001	51.7±16.9	39.2±15.1	<0.001
LV ejection fraction (%)*	68.2±10.1	61.1±9.07	<0.001	67±7.1	66±9.5	0.248
Doppler measurements of the left ventricle						
E (cm/s)*	98.8±24.4	63.4 ± 21.3	<0.001	97.7±25.4	67.9±23.8	<0.001
A (cm/s)*	83.8±25.7	78.8 ± 30.6	0.332	80±28.0	72.2±32.7	0.114
E/A*	1.2±0.5	0.8 ± 0.3	<0.001	1.3±0.4	0.9±0.4	0.004
Deceleration time (ms)*	186.1±43.7	222.6 ± 92.1	0.024	184.8±64.6	203.6±50.9	0.125
Tissue Doppler measurements of the left ventricle						
$E'_{lateral}$ (cm/s)*	12.2±3.6	9.5±2.6	0.001	12.8±4.4	10.5±3.8	<0.001
$A'_{lateral}$ (cm/s)*	11.4±3.4	10.4± 2.8	0.144	11±2.5	10.4±2.8	0.202
$S'_{lateral}$ (cm/s)*	13.7±3.9	10.7±3.4	<0.001	11.6±2.1	10.6±2.6	0.035
$E/E'_{lateral}$*	9.0±3.4	7.3±3.3	0.003	8.5±3.8	7.2±3.2	0.004
E'_{septal} (cm/s)*	10.3±3.7	7.6±2.1	0.001	10±3.6	8.3±2.7	0.001
A'_{septal} (cm/s)*	10.4±2.6	10.5±3	.847	10.3±2.4	10.1±2.7	0.611
S'_{septal} (cm/s)*	12.5±2.1	9.4±3	0.001	11.7±2	9.8±2	0.736
E/E'_{septal}*	9.1±3.7	7.1±3.4	0.008	8.7±3.0	7.5±3.4	0.035

*Paired t-test was used.
AUR - acceptable ultrafiltration rate; HD - hemodialysis; HUR - high ultrafiltration rate; LV - left ventricle

Table 5. Two-dimensional speckle-tracking strain measurements of the right ventricle and left ventricle before and after hemodialysis

Parameters	Group HUR (n=23)		*P*	Group AUR (n=42)		*P*
	Before HD	After HD		Before HD	After HD	
Deformation parameters						
RV GLS (%)*	-24.1±3.7	-17.8±4.5	<0.001	-24.5±3.7	-20.9±3.7	<0.001
LV GLS (%)*	-21.5±3.8	-16.3±3.3	<0.001	-21.4±2.8	-18.2±3.5	0.001
RV FW LS (%)*	-27.8±4.2	-21±5.3	<0.001	-29.5±5	-25.1±5.2	<0.001
RV mechanical dispersion[¥] (ms)	26 (14-40)	42 (18-52)	<0.001	23 (12-36)	32 (14-38)	0.078
LV mechanical dispersion[¥] (ms)	30 (18-45)	38 (19-50)	0.108	30 (16.48)	35 (17-48)	0.200

*Paired t-test was used.
[¥]Wilcoxon t-test was used.
AUR - acceptable ultrafiltration rate; FW - free wall; GLS - global longitudinal strain; HD - hemodialysis; HUR - high ultrafiltration rate; LS - longitudinal strain; LV - left ventricle; RV - right ventricle

terms of defining high-risk patients for sudden cardiac death in order to prevent unnecessary interventions. Electrophysiologists are still searching for novel promising predictors as clinical and echocardiographic, biochemical variables (27). 2D speckle-tracking echocardiography is used to measure the timing of segmental myocardial shortening and its synchronicity by mechanical dispersion. Prolonged mechanical dispersion is proposed as a risk predictor in patients with structural heart diseases that reveals temporal heterogeneity of myocardial contraction (14, 16, 18, 21, 34, 35). Age, GLS, and E/e′ ratio have been recently determined as physiological determinants of mechanical dispersion (36). Future studies are needed to verify and to clarify whether the concept of mechanical, electrical, and histological differences may constitute prognostic information in diverse cardiac conditions. We have found a significant increase in RV mechanical dispersion, but not in LV mechanical dispersion. The possible reasons of this finding could be the different responses of the ventricle to pressure and volume changes by having different wall thicknesses and wall stress. The presence of hypervolemia and inappropriate volume depletion during HD may result in rapid reduction of myocardial stretch that can cause myocardial dyssynchrony temporarily. Moreover, the rapid change in RV geometry due to reduction of pressure or volume overload may cause an impaired alignment of the myocardial fibrils that can contribute to heterogeneity of mechanical synchrony. The undesirable impact of rapid volume depletion on RV dyssynchrony may be ameliorated gradually.

Patients with end-stage kidney disease are observed to be at risk of serious arrhythmias. LV mechanical dispersion is proposed as a risk predictor of fatal arrhythmias in patients with chronic kidney disease (18). Thus, rapid ultrafiltration causing RV mechanical dispersion can have a possible arrhythmogenic influence that should be validated with further investigations.

Clinical perspective of findings

High ultrafiltration rate and volume are strongly associated with cardiovascular adverse events. Ultrafiltration rate–cardiovascular outcome relationship is well-demonstrated in mechanistic studies, whereas observational studies have some contradictory results with some limitations (7, 9, 37-48). Vital organ hypoperfusion due to ultrafiltration-induced hypotension was the outcome predictor among these patients. Reduced coronary flow, cardiac ischemia along with myocardial stunning, and troponin elevation are the results of ultrafiltration-induced volume depletion in the cardiovascular system (2, 6-8, 41, 42, 49). Although it is difficult, further studies are needed in order to determine the exact correlation between ultrafiltration rates and other fluid measurements, such as weight gain and volume expansion. Epidemiologic findings need to be confirmed with randomized trials. Optimal fluid management is a matter of debate as there are many accumulating data about fluid-related factors. Standardized fluid management cannot be implemented because objective volume status parameters are lacking. Thus, ultrafiltration rate may serve as an objective value and can be taken into account for optimal fluid management (1). Additionally, with the present study, we showed that HUR significantly affect RV mechanical dispersion. In addition, the difference observed in RV mechanical dispersion might have clinical implications because higher mechanical dispersion and asynchronicity of the RV were associated with increased arrhythmogenicity in other pathologic substrates. Thus, increased arrhythmogenicity might be a cause of higher mortality among these patients (50). Based on our argument, a future follow-up study would be of interest to confirm these clinical implications. Nevertheless, ultrafiltration rates and volumes should be restricted for hemodynamic stability and tolerability; additional HD sessions may be needed when excessive volume load is detected according to the up-to-date guidelines. Additional HD sessions should be considered for patients with extensive volume overload (1, 42).

Study limitations

In our study, invasive heart catheterization for the assessment of chamber pressures could not be performed since it is an interventional procedure and was not indicated. The documentation of arrhythmias before, after, and during HD is lacking with either resting 12-lead electrocardiography (ECG) or 24-hour Holter ECG monitoring that is another limitation of our study. Electrolyte changes during HD may have an impact on our results by affecting myocardial contractility and cardiac action potential; unfortunately, these values are not available in our study. Nevertheless, we have investigated the overall impact of HD on mechanical dispersion so we believe to present reliable results on the subject. We did not have the chance to evaluate the impact of increasing RV mechanical dyssynchrony on long-term cardiac outcomes since this was a cross-sectional study.

Conclusion

In conclusion, we showed in our study that rapid ultrafiltration can cause RV mechanical dispersion. Ultrafiltration rate and volume should be personalized, and additional HD sessions should be performed to avoid cardiac impairment.

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