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Original Investigation

Echocardiographic Parameters During Long and Short Interdialytic Intervals in Hemodialysis Patients

Konstantinos Tsilonis, MD,[1] Pantelis A. Sarafidis, MD, MSc, PhD,[2,3] Vasilios Kamperidis, MD, MSc, PhD,[1] Charalampos Loutradis, MD, MSc,[2] Panagiotis I. Georgianos, MD, PhD,[3] Konstantinos Imprialos, MD,[2] Antonios Ziakas, MD, PhD,[1] Georgios Sianos, MD, PhD,[1] Pavlos Nikolaidis, MD, PhD,[3] Anastasios N. Lasaridis, MD, PhD,[3] and Haralambos Karvounis, MD, PhD[1]

Background: The long interdialytic interval in thrice-weekly hemodialysis is associated with excess cardiovascular risk. However, the mechanisms behind these adverse consequences are not fully understood. This study investigated the interdialytic changes in right and left ventricular function during the 2- and 3-day intervals.

Study Design: Observational study with 2 random crossover sequences of recordings: 3-day followed by 2-day interval or vice versa.

Settings & Participants: 41 stable patients with end-stage renal disease on standard thrice-weekly hemodialysis therapy.

Predictor: 3-day (long) versus 2-day (short) interdialytic interval.

Outcome: Interdialytic change in echocardiographic indexes of left and right ventricular function.

Measurements: 2-dimensional echocardiographic and tissue Doppler imaging studies were performed with a Vivid 7 cardiac ultrasound system at the start and end of the 3- and 2-day interdialytic intervals.

Results: During both intervals studied, elevations in cardiac output, stroke volume, left ventricular mass index, and peak early diastolic velocities of the left ventricle were evident. Interdialytic weight gain (3.0 $\pm$ 1.7 vs 2.4 $\pm$ 1.3 [SD] kg) and inferior vena cava diameter increase (0.54 $\pm$ 0.3 vs 0.25 $\pm$ 0.3) were higher during the 3-day versus the 2-day interval ($P < 0.001$). Left ventricular systolic and diastolic function indexes were generally no different between interdialytic intervals. In contrast, interdialytic increases in left and right atrial volume, right ventricular systolic pressure (RVSP; 15.3 $\pm$ 10.2 vs 4.7 $\pm$ 5.2 mm Hg; $P < 0.001$), and tricuspid regurgitation maximum velocity (0.46 $\pm$ 0.45 vs 0.14 $\pm$ 0.33 m/s; $P = 0.001$) were significantly greater during the 3- versus the 2-day interval. Multivariable analysis suggested that changes in interdialytic weight gain, right ventricle diastolic function, and pulmonary vascular resistance were determinants of the change in RVSP.

Limitations: Observational study design.

Conclusions: Excess volume accumulation over the long interdialytic interval in hemodialysis patients results in higher left and right atrial enlargement and RVSP elevation, which clinically corresponds to pulmonary circulation overload, providing one plausible pathway for the excess mortality risk during this period.
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INDEX WORDS: Long interdialytic interval; hemodialysis; volume excess; atrial enlargement; right ventricular systolic pressure (RVSP); pulmonary circulation overload; echocardiography; end-stage renal disease (ESRD); cardiovascular risk.

Patients with end-stage renal disease (ESRD) receiving hemodialysis have one of the highest rates of cardiovascular morbidity and mortality.[1,2] Among hemodialysis patients, serious arrhythmias and sudden cardiac arrests rather than ischemic cardiac and cerebrovascular events are the most frequent causes of cardiovascular death.[3] This is possibly attributable to an arrhythmogenic cardiac substrate of hemodialysis patients related to increased arterial stiffness, left ventricular (LV) hypertrophy, and intermyocardiocytic fibrosis.[4] Other predisposing factors are suggested to be intra- and interdialytic shifts in volume status, electrolyte balance, and metabolic parameters due to the intermittent nature of renal replacement therapy and inherent reduced capacity of patients with ESRD for urinary fluid, electrolyte, and uremic toxin excretion.[5,6]

In most parts of the developed world, hospital- or unit-based maintenance hemodialysis is typically prescribed in a thrice-weekly schedule with a short

From the [1]1st Department of Cardiology, AHEPA Hospital, [2]Department of Nephrology, Hippokration Hospital, and [3]Section of Nephrology and Hypertension, 1st Department of Medicine, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.

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Address correspondence to Pantelis A. Sarafidis, MD, MSc, PhD, Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Konstantinoupoleos 49, GR54642, Thessaloniki, Greece. E-mail: psarafidis11@yahoo.gr

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interdialytic interval (~2 days) prior to the second and third dialysis treatment of the week and an asymmetrically longer interval (~3 days) before the first weekly dialysis session. During the past few years, a growing body of evidence derived from large-scale population data supports that mortal events and cardiovascular-related hospitalizations are not evenly distributed throughout the days of the week, but more commonly occur within the last hours of the 3-day interval and the following dialysis session, that is, they are 25% to 40% higher during the first dialysis day of the week (Monday or Tuesday) compared to any other day of the week.[7-10]

Although the link between the long interdialytic interval and worsened cardiovascular outcomes has attracted increasing attention, the mechanistic background of this association is not fully clear. We have previously shown that the 3-day interdialytic interval imposes a significant increase in central aortic blood pressure (BP) and wave reflection indexes, an effect that was closely associated with interdialytic weight gain (IDWG).[11,12] It therefore could be hypothesized that higher LV preload as a result of excess volume accumulation at the end of the 3-day interval may acutely worsen cardiac function. However, echocardiographic studies to evaluate changes in systolic and diastolic heart function in relation to changes in volume status over the 3- and 2-day interdialytic intervals are currently limited. Therefore, the aim of the present study was to investigate in patients with ESRD receiving standard thrice-weekly hemodialysis whether: (1) echocardiographic indexes of systolic and diastolic cardiac function are changed during the interdialytic intervals and (2) interdialytic changes in these parameters differ between the long (3-day) and regular (2-day) dialysis-off periods.

METHODS

Study Population

Patients receiving maintenance hemodialysis therapy in the Hemodialysis Unit of AHEPA University Hospital were invited to participate if they fulfilled the inclusion and exclusion criteria. Inclusion criteria consisted of: (1) 18 years or older; (2) standard renal replacement schedule with 3 dialysis sessions per week; (3) dialysis vintage of at least 3 months; and (4) dialysis adequacy with single-pool $Kt/V > 1.2$. Patients were excluded from the study in case of: (1) myocardial infarction, unstable angina, or stroke during the previous 6 months; (2) severe stage III to IV congestive heart failure according to the New York Heart Association classification; (3) chronic atrial fibrillation or other known arrhythmia; (4) history of nonadherence to the prescribed weekly dialysis schedule in the previous month; (5) body mass index $\geq 40\ kg/m^2$; or (6) history of malignancy or other clinical condition associated with very poor prognosis. Of all patients receiving maintenance dialysis in our unit (78 patients), 61 met the inclusion and exclusion criteria and 44 volunteered to participate in the study. Of them, 3 patients did not perform the echocardiographic assessment at all sequence of study visits; thus, 41 patients with complete data sets were included in the present analysis.

The research protocol was approved by the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki (Nr: A13761/31.8.2010), and all patients provided informed written consent prior to study enrollment. All protocol procedures performed in the study were in accordance with the ethical standards of the institutional Ethics Committee and with the Declaration of Helsinki (2000 Amendment).

Study Procedures

Demographic characteristics, full medical history, and dialysis-related parameters of study participants were recorded on purpose-built data collecting sheets. Study participants, among others, were evaluated over a 5-day period covering 3 consecutive dialysis sessions in order to capture changes in echocardiographic indexes over the 3- and 2-day interdialytic intervals. The study design diagram presenting the chronologic sequence of the 4 echocardiography evaluations is presented in Fig 1. Patients were randomly assigned to 2 groups with different order of recordings (crossover). In the first group (Fig 1A), patients had measurements performed at start and end of the 3-day followed by measurements at the start and end of the 2-day interval. In detail, patients were studied on Friday or Saturday, 30 minutes after the end of the third dialysis session of the first week (visit 1); Monday or Tuesday, respectively, 30 minutes before the first dialysis session of the second week (visit 2); Monday or Tuesday, respectively, 30 minutes after the end of the first dialysis session of the second week (visit 3); and Wednesday or Thursday, respectively, 30 minutes prior to the midweek dialysis session (visit 4). In the second group (Fig 1B), we captured the parameters of interest of the 2-day followed by the 3-day interval at similar time points before and after the relevant dialysis sessions. For reasons of clarity, all data presented here follow the order of measurements of the first group (3-day followed by 2-day interval).

At each study visit, weight and height were recorded in order to calculate body mass index and body surface area using the Du Bois and Du Bois[13] formula. Brachial BP was recorded at the nonfistula arm with the use of a conventional sphygmomanometer, according to current international guidelines.[14] Subsequently, a comprehensive transthoracic echocardiographic study, including 2-dimensional grey scale images, color, tissue, pulse wave, and continuous wave Doppler data, was performed at each study visit by a dedicated experienced physician with the use of a commercially available cardiac ultrasound system (Vivid 7 or Vivid e; GE). All echocardiographic data were stored digitally and analyzed offline by another experienced physician blinded to the time points of each study. At each dialysis day, patients underwent their regular hemodialysis treatment, during which ultrafiltration volume was programmed according to their prespecified dry weight, estimated by standard clinical criteria. Changes in dry weight throughout the 2-week study period were prohibited by protocol. In addition, study participants were instructed to maintain their usual habits, including food and water intake during the interdialytic periods.

Echocardiographic Data Analysis

The echocardiographic parameters studied are presented in Box 1. On 2-dimensional grey scale images, in the parasternal long-axis view, LV systolic and diastolic dimensions and end-diastolic thickness of the interventricular septum and LV posterior wall were measured. LV ejection fraction was calculated from LV end-diastolic and end-systolic volumes using the biplane Simpson's method.[15] LV mass index (LVMi) was calculated according to the cube formula based on recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging.[15] Left atrial (LA) volumes were calculated from the apical 4- and 2-chamber views with the biplane method of disks and were indexed for body surface area. Peak early diastolic velocity (E),