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Effect of Frequent or Extended Hemodialysis on Cardiovascular Parameters: A Meta-analysis

Paweena Susantitaphong, MD^{1,3,4}, Ioannis Koulouridis, MD^{1,3}, Ethan M. Balk, MD, MPH^{2,3}, Nicolaos E. Madias, MD, FASN^{1,3}, and Bertrand L. Jaber, MD, MS^{1,3}

¹Department of Medicine, Division of Nephrology, Kidney and Dialysis Research Laboratory, St. Elizabeth's Medical Center, Boston, MA ²Center for Clinical Evidence Synthesis, Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA ³Department of Medicine, Tufts University School of Medicine, Boston, MA ⁴Extracorporeal Multiorgan Support Dialysis Center, Division of Nephrology, Department of Medicine, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Abstract

Background—Increased left ventricular (LV) mass is a risk factor for cardiovascular mortality in patients with chronic kidney failure. More frequent or extended hemodialysis (HD) has been hypothesized to have a beneficial effect on LV mass.

Study Design—Meta-analysis.

Setting & Population—MEDLINE literature search (inception-April 2011), Cochrane Central Register of Controlled Trials and ClinicalTrials.gov using the search terms “short daily HD”, “daily HD”, “quotidian HD”, “frequent HD”, “intensive HD”, “nocturnal HD”, and “home HD”.

Selection Criteria for Studies—Single-arm cohort studies (with pre- and post-study evaluations) and randomized controlled trials examining the effect of frequent or extended HD on cardiac morphology and function, and blood pressure parameters. Studies of hemofiltration, hemodiafiltration and peritoneal dialysis were excluded.

Intervention—Frequent (2–8 hours, > thrice weekly) or extended (>4 hours, thrice weekly) HD as compared with conventional (<4 hours, thrice weekly) HD.

Outcomes—Absolute changes in cardiac morphology and function, including LV mass index (LVMI) (primary), and blood pressure parameters (secondary).

Results—We identified 38 single-arm studies, 5 crossover trials and 3 randomized controlled trials. By meta-analysis of 23 study arms, frequent or extended HD significantly reduced LVMI from baseline (−31.2 g/m², 95% CI, −39.8 to −22.5; P<0.001). The 3 randomized trials found a less pronounced net reduction in LVMI (−7.0 g/m²; 95% CI, −10.2 to −3.7; P<0.001). LV ejection fraction improved by 6.7% (95% CI, 1.6 to 11.9; P=0.01). Other cardiac morphological parameters

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Address for Correspondence: Bertrand L. Jaber, MD, MS, St. Elizabeth's Medical Center, 736 Cambridge Street, Boston, MA 02135, Phone: (617) 562-7832 | Facsimile: (617) 562-7797, bertrand.jaber@steward.org.

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displayed similar improvements. There were also significant decreases in systolic, diastolic, and mean blood pressure, and mean number of anti-hypertensive medications.

Limitations—Paucity of randomized controlled trials.

Conclusions—Conversion from conventional to frequent or extended HD is associated with an improvement in cardiac morphology and function, including LVMI and LV ejection fraction, respectively, and in several blood pressure parameters, which collectively might confer long-term cardiovascular benefit. Trials with long-term clinical outcomes are needed.

Keywords

frequent HD; extended HD; conventional HD; LVMI; meta-analysis

Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD) treated with dialysis¹. Increased left ventricular (LV) mass (LVM), also referred to as left ventricular hypertrophy (LVH), is an independent predictor of cardiovascular morbidity and mortality in the general population and in patients with CKD^{2,3}. The prevalence of LVH increases with declining kidney function⁴. Most patients with kidney failure eventually develop LVH due to longstanding hypertension and extracellular-fluid volume expansion, and possibly as a result of the retention of uremic solutes with cardiac remodeling properties⁵.

Echocardiographic or magnetic resonance imaging (MRI) estimates of the LVM (in g) are usually indexed to body surface area, yielding the LVM index (LVMI, in g/m²). Previous studies of anti-hypertensive medications have demonstrated that LVH regression, as measured by a reduction in the LVMI, has a favorable and independent effect on all-cause and cardiovascular mortality in the general population⁶ as well as in patients with CKD treated with dialysis⁷. Conventional in-center hemodialysis (HD) (< 4 hour session length, thrice weekly) is associated with substantial fluctuations in the extracellular-fluid volume and serum electrolytes. Frequent (2–8 hour session length, > thrice weekly) and extended (> 4 hour session length, thrice weekly) HD might provide better control of the extracellular-fluid volume and blood pressure as well as the removal of putative molecules involved in cardiac remodeling, which in turn, might result in better cardiovascular outcomes compared to conventional HD. Commonly employed frequent HD regimens include short daily HD (2–3 hour session length, 5–6 days per week) and nocturnal HD (6–8 hour session length, 5–6 days per week), whereas extended HD is typically delivered as a 6–8 hour session length, 3 days per week.

We conducted a meta-analysis to examine the potential benefits of frequent or extended HD on cardiac morphology and function, including LVMI, and blood pressure parameters.

METHODS

Data Sources and Searches

We performed a MEDLINE literature search (inception–April 2011) to identify eligible studies using the search terms “short daily hemodialysis”, “daily hemodialysis”, “quotidian hemodialysis”, “frequent hemodialysis”, “intensive hemodialysis”, “nocturnal hemodialysis”, and “home hemodialysis”. The search was limited to human studies. We also searched the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov for completed studies using similar search terms, and reviewed the *American Society of Nephrology* abstracts (2003–2010 meetings), as well as the bibliographies of retrieved articles and of a primer in frequent HD provided by a manufacturer of home dialysis equipment (www.nxstagemedical.com).

Study Selection

We included single-arm cohort studies (with pre- and post-study evaluations) and randomized controlled trials examining the effect of frequent or extended HD on cardiac morphology and function, and blood pressure parameters. Studies of hemofiltration, hemodiafiltration and peritoneal dialysis were excluded. The primary cardiac parameter of interest was the change in the mean LVMI, as measured by echocardiography or cardiac MRI. Other cardiac morphological and functional parameters that we assessed were the changes in the mean LVM, LV systolic diameter (LVSD), LV end-diastolic diameter (LVEDD), LV posterior wall (LVPW) thickness, intra-ventricular septum (IVS) thickness, left atrium end-diastolic diameter (LAEDD), and LV ejection fraction (LVEF). The blood pressure parameters of interest were changes in the mean systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and number of anti-hypertensive medications, as well as the percentage of patients not taking anti-hypertensive medications. There were no restrictions on language, sample size, or duration of follow-up. Two authors (PS and IK) independently screened the titles and abstracts of all electronic citations. The full-text articles were retrieved for comprehensive review and were independently re-screened.

Data Extraction and Quality Assessment

The following data were extracted: country of origin, year of publication, study design, sample size, percentage of men, mean age, mean duration of dialysis, and prevalence of hypertension. Frequent or extended HD prescription variables were also extracted, including frequency per week (in days), session duration (in hours), total weekly hours of HD, and duration of intervention (in months). The studies were arbitrarily grouped into 3 study duration categories: 1–6 months, 7–12 months, and > 12 months.

For assessment of cardiac morphology and function, we extracted data on the imaging acquisition technique (echocardiography *vs.* cardiac MRI) and on reader variability (blinded *vs.* non-blinded observer). For studies not reporting the mean LVM or LVMI, the mean LVM was first calculated using the following equation provided by the American Society of Echocardiography⁸: $LVM = 0.8 \times 1.04 \times [(LVEDD + IVS + LVPW)^3 - LVEDD^3] + 0.6$. The mean LVMI (in g/m²) was then calculated by normalizing the mean LVM to the mean body surface area. If not reported, the mean body mass index was calculated using the provided mean weight and height⁹. If the height was not reported, we used the study country-specific mean height derived from the Dialysis Outcomes and Practice Patterns Study (DOPPS)¹⁰.

Similarly, for assessment of the blood pressure parameters, we extracted data on the technique used to measure blood pressure (mechanical [e.g., mercury or aneroid] or digital sphygmomanometry, *vs.* ambulatory blood pressure monitoring), use of trained personnel (*vs.* self-reporting) and number of blood pressure recordings at each measurement (i.e., single *vs.* average of several recordings).

Where indicated, the G3data graph analyzer (version 1.5.3) was used to extract data from graphs. Disagreements were resolved through consensus and arbitration by a third author (BLJ). Corresponding authors of 7 studies were contacted for data clarification. The quality of the cohort studies was assessed using the Newcastle-Ottawa Scale¹¹. The Jadad score was used to assess the quality of the randomized controlled trials.

Data Synthesis and Analysis

Since the search yielded primarily single-arm or cohort studies and only 3 parallel-arm randomized controlled trials, we conducted random-effects model meta-analyses on pre-post changes in cardiac morphology, cardiac function, and blood pressure parameters, following

conversion from conventional HD to frequent or extended HD (irrespective of duration of follow-up and study design)¹². For non-randomized crossover trials, we used the data from the first period; for randomized crossover trials, we first extracted the mean values at the end of each arm period and then calculated the change between the 2 study arms; and for randomized controlled trials, we used only the experimental study arm. If the standard error of the change was not reported, we assumed a 50% correlation between the baseline and final values when estimating the standard error of the change.

For the parallel-arm randomized controlled trials, we performed random-effects model meta-analyses to assess the net change in cardiac morphology and function, blood pressure parameters, and the odds ratio for all-cause mortality in the frequent or extended HD-treated group relative to the conventional HD-treated group. We imputed the missing standard deviations in 8 studies with the median value calculated from the remaining studies for the same measurement period.

Existence of heterogeneity among effect sizes estimated by individual studies was assessed using the I^2 index, and the chi-square test. An I^2 index $\geq 50\%$ was used to indicate medium-to-high heterogeneity¹³. We investigated the heterogeneity of studies for the outcome changes in LVMI, SBP, and number of anti-hypertensive medications with univariate random-effect model meta-regression based on a priori selected categorical study characteristics: modality (frequent vs. extended HD); duration of follow up (1–6, 7–12, and >12 months); study quality; cardiac imaging acquisition technique, and reader blinding (for the LVMI outcome); and blood pressure reader technique (for the SBP outcome). Duration of follow-up was also analyzed as a continuous variable. The meta-analyses were performed using Comprehensive Meta-Analysis version 2.0 and Stata 11 (College Station, TX) where we used the metan and metareg commands. Publication bias was assessed with funnel plots.

RESULTS

Study Characteristics

A total of 2,813 potentially relevant citations were identified and screened; 82 articles were retrieved for detailed evaluation, of which 46 fulfilled eligibility criteria (Figure 1)^{14–59}, representing 38 single-arm or cohort studies, 2 randomized crossover trials, 3 non-randomized crossover trials, and 3 parallel-arm randomized controlled trials. Five single-arm studies reporting on 2 different frequent or extended HD prescriptions were analyzed separately^{21,25,33,43,45}.

Characteristics of the individual studies are displayed in Table 1. The studies spanned more than 20 years, varied in sample size (4–247 patients) and involved the 3 HD prescriptions. Mean age ranged from 35–67 years, mean dialysis duration from 4–172 months, and prevalence of hypertension from 17–100%.

Twenty-three studies assessed at least one cardiac morphological or functional parameter. The cardiac parameters were evaluated by unspecified mode echocardiography in 11 studies, M-mode echocardiography in 9 studies, and cardiac MRI in 3 studies. Blinded readers assessed the cardiac structures in only 9 studies, whereas 14 studies did not specify the mode of assessment. Among 6 studies that used M-mode echocardiography, the assessment was performed midweek either on the day of the scheduled treatment pre-dialysis or during the inter-dialytic period on a non-dialysis day. For all other studies, the timing of the study in relation to dialysis was not specified.

Thirty-five studies assessed systolic blood pressure. The blood pressure was measured pre-dialysis by mercury sphygmomanometry in 7 studies and digital sphygmomanometry in 2

studies, and during the inter-dialytic period by ambulatory blood pressure monitoring in 6 studies. The remaining 20 studies did not specify how the blood pressure was measured. Nineteen studies used an average of several blood pressure recordings at each measurement, which were obtained by trained personnel, whereas 16 studies did not specify the frequency of blood pressure recordings.

According to the Newcastle Ottawa Scale, most cohort studies were considered of fair (scale of 4–6) to good (scale of 7–9) quality (Table 1). For the 3 randomized controlled trials, the Jadad score were 3.

Effect of Frequent or Extended HD on Cardiac Morphology and Function

In an analysis of 23 study arms or cohorts that assessed LVMI (524 analyzable patients), the baseline mean LVMI, by meta-analysis, was 155.7 g/m² (95% CI, 109.4–135.2). Conversion from conventional HD to frequent or extended HD resulted in a significant reduction in the LVMI (–31.2 g/m²; 95% CI, –39.8 to –22.5; $P<0.001$; Figure 2). In the 3 randomized controlled trials, a smaller net reduction in the LVMI was observed (–7.0 g/m²; 95% CI, –10.2 to –3.7; $P<0.001$)^{50,57,59}.

In an analysis of 13 study arms that reported on LVM (335 analyzable patients), frequent or extended HD resulted in a significant reduction in the LVM (–60.5 g; 95% CI, –90.8 to –30.2; $P<0.001$). A smaller net reduction in the LVM was observed in the 3 randomized controlled trials (–13.4 g; 95% CI, –19.5 to –7.4; $P<0.001$)^{50,57,59}.

In an analysis of the 4 studies that reported on LVEF (137 analyzable patients), frequent or extended HD resulted in a significant increase in the LVEF of 6.7% (95% CI, 1.6–11.9; $P=0.01$). Finally, the beneficial effect of frequent or extended HD on other indices of cardiac chambers including changes in the LVSD, LVEDD, LVPW thickness, IVS thickness, and LAEDD are summarized in Table 2, and demonstrate a significant improvement in all parameters. Selected forest plots displaying the effect of frequent or extended hemodialysis on change in LAEDD, LVEF, SBP, and number of anti-hypertensive medications are displayed in Figures S1–S4 (available as online supplementary material). There was substantial heterogeneity among effect sizes as measured by the I^2 index, which was 50% in most of the analyses, indicating medium-to-high heterogeneity, as well as by the Chi-square P -value with the exception of the analysis on changes in the IVS thickness and LAED.

Effect of Frequent or Extended HD on Blood Pressure Parameters

In an analysis of 35 study arms that assessed SBP (928 analyzable patients), frequent or extended HD resulted in a significant reduction (–14.1 mmHg; 95% CI, –17.2 to –11.0; $P<0.001$). A smaller net reduction in SBP was observed in the 3 randomized controlled trials (–10.1 mm Hg; 95% CI, –13.5 to –6.6; $P=0.001$)^{50,57,59}. The effects of frequent or extended HD on other blood pressure parameters are summarized in Table 2. In brief, DBP changed by –7.1 mm Hg (95% CI, –9.2 to –4.9; $P<0.001$) and MAP by –11.8 mmHg (95% CI, –13.8 to –9.8; $P<0.001$), respectively. The mean number of anti-hypertensive medications decreased by an average of 0.8 (95% CI, –1.2 to –0.5; $P<0.001$), and by the end of the follow up period, 53.5% (95% CI, 42.9–63.8) of patients were not taking anti-hypertensive medications. There was substantial heterogeneity among effect sizes based on the I^2 index and the Chi-square P -value.

Effect of Frequent or Extended HD on All-Cause Mortality

An exploratory analysis restricted to the 3 trials of frequent HD^{50,57,59} with 383 analyzable patients revealed a pooled odds ratio of 0.74 for all-cause mortality (95% CI, 0.28–1.96; $P=0.3$). The I^2 index was 0% and the chi-square P -value was 0.4.

Investigations of heterogeneity

Figure 3 displays the meta-regression analyses exploring the change in LVMI stratified by duration of follow-up, cardiac imaging acquisition technique, and reader blinding. As shown in Figure 3A, the duration of follow-up was associated with a progressively larger reduction in the LVMI, although this was not a statistically significant factor either as a categorical or continuous variable ($P=0.2$). However, studies utilizing cardiac MRI displayed a less robust improvement in LVMI compared to studies utilizing M-mode echocardiography ($P=0.009$; Figure 3B) or unspecified mode echocardiography mode ($P<0.001$; Figure 3B). In addition, studies employing blinded readers were associated with a predictably less robust improvement in LVMI ($P=0.005$; Figure 3C).

The changes in the SBP and number of anti-hypertensive medications were not significantly different as a function of duration of follow-up ($P=0.9$ and 0.8 , respectively; Figures 4A and 4B). The SBP did not further fall and the mean number of anti-hypertensive medications did not further decrease beyond the first 6 months of therapy, suggesting a plateau effect. Meta-regression analyses according to the blood pressure measurement technique, use of trained personnel (vs. self-reporting), number of blood pressure recordings at each measurement (i.e., single vs. average of several recordings) did not reveal significant difference in SBP change.

Meta-regression analyses according to the quality of the cohort studies did not yield significant differences in LVMI or number of anti-hypertensive medications (data not shown). There were too few randomized controlled trials to perform meta-regression analyses according to the Jadad score. Funnel plots for the difference in means of LVMI, SBP, and number of anti-hypertensive medications were symmetric (Figures S5–S7).

DISCUSSION

In the present meta-analysis, we demonstrate that frequent or extended HD is associated with a significant improvement in several measures of cardiac morphology, including the LVMI, an important intermediate cardiovascular endpoint with well-established prognostic value in this patient population. There was also a significant improvement in the LVEF, an important cardiac functional index, and several blood pressure parameters, including an improvement in the systolic and diastolic blood pressures, and a decrease in the mean number of anti-hypertensive medications. These observations remained significant across single arm studies and randomized controlled trials, and across a range of meta-regression analyses aimed at exploring heterogeneity.

Hemodialysis remains the most commonly used treatment modality for end-stage kidney disease worldwide. Despite technological advances in the delivery of HD and the widespread adoption of clinical practice dialysis guidelines⁶⁰, the mortality of patients with CKD treated by conventional HD remains alarmingly high¹. This inordinate mortality implies that the delivery of HD in its most prevalent current format is suboptimal and has failed to improve clinical outcomes⁶¹. Unconventional dialysis regimens, including short daily and longer nocturnal HD, have been regaining popularity in recent years^{62,63}, with the perceived notion that these therapies might better approximate renal physiology and improve clinical outcomes.

Cardiovascular disease is the leading cause of death in patients with kidney failure¹. Increased LVM or LVMI is a known modifiable cardiovascular risk factor, especially in the dialysis population^{64,65}. Important determinants of LVM include hemodynamic and non-hemodynamic factors. In the dialysis population, the most salient hemodynamic parameters are the high prevalence of hypertension, extracellular-fluid volume expansion, anemia, and the presence of arteriovenous shunts^{66,67}. Indeed, a direct correlation between inter-dialytic weight gains and LVM has previously been demonstrated⁶⁴. In recent years, frequent HD regimens have extensively been studied; mainly short daily HD (2–3 hour session length, 5–6 days per week) and nocturnal HD (6–8 hour session length, 5–6 days per week)^{68,69}. Two of the 3 recently completed randomized controlled trials have demonstrated that compared to conventional HD, both short daily HD and nocturnal HD improve blood pressure control and lead to LVH regression^{50,57}; the third trial of frequent nocturnal HD failed to demonstrate a net improvement in the LVM despite a significant net improvement in the SBP⁵⁹. Increasing of vascular access-related events in the nocturnal HD study arm might have accounted for these differences in outcomes.

Non-hemodynamic factors that might influence the LVM in the dialysis population include the retention of molecules with putative cardiac remodeling properties. In experimental settings, angiotensin II, endothelin, and insulin-like growth factors promote cardiac hypertrophy^{70,71}. Since circulating levels of these trophic factors might be elevated in patients with kidney failure⁷², we can only speculate as to whether frequent or extended HD might enhance their removal. Compared to conventional HD, frequent HD regimens have recently been shown to be associated with lower ultrafiltration volumes and less dialysis-induced myocardial stunning, as defined by a reduction in intradialytic echocardiographic LV regional wall motion abnormalities.⁷³ Moreover, nocturnal HD was shown to be associated with a return to function of early-outgrowth endothelial progenitor-like cells, which might affect cardiac remodeling⁷⁴. These considerations support the hypothesis that improvement in LVM in patients with kidney failure treated with these alternative dialysis regimens might indeed reflect the long-term salutary effect on several hemodynamic and non-hemodynamic factors. However, as demonstrated in a recent trial⁵⁹, these potential benefits might be offset by vascular access-related events, resulting in increased morbidity.

In trials of anti-hypertensive agents performed in the general population, LVH regression, as measured by the LVM or LVMI, has been shown to improve the LV systolic and diastolic function, improve coronary reserve, and reduce the incidence of cardiac arrhythmias⁷⁵. Therefore, the use of this surrogate endpoint in the 3 recently completed largest trials of frequent HD is well justified^{50,57,59}. In a study of patients on conventional HD receiving treatment for hypertension, a 10% decrease in the LVM was associated with a 22% and 28% risk reduction in all-cause and cardiovascular mortality⁷. In our meta-analysis, we observed a 25% mean decrease in the LVM, as well as an improvement in the LVEF by 6.7 percentage points, arguing for a potential long-term cardiovascular survival benefit of frequent or extended HD.

In addition to improvements in the LVMI and LVEF, two important morphological and functional cardiac indices, we also observed an improvement in several other cardiac morphological parameters, including the LAEDD. An LAEDD of greater than 40 mm has been shown to predict the development of atrial fibrillation in patients treated with conventional HD, and is an important predictor of lack of response to medical therapy^{76,77}. This is noteworthy, in light of the increasing prevalence of atrial fibrillation in the HD population^{64,77,78}. Atrial fibrillation is the most common cardiac arrhythmia in patients receiving HD and is associated with increased mortality^{77,78}. The identification of potentially modifiable risk factors of this arrhythmia is imperative. In our meta-analysis, the baseline mean LAEDD was 40.7 mm (95% CI 38.0, 43.4). We can only speculate as to

whether the left atrial remodeling that is associated with frequent or extended HD would result in a lower incidence of atrial fibrillation.

Strengths of our synthesis include the large sample size, and the demonstrable benefit of frequent or extended HD on all measures of cardiac morphology, cardiac function, and blood pressure parameters. Although we observed an improvement in these surrogate endpoints, we were unable to demonstrate a survival benefit of these alternative dialysis regimens in an analysis restricted to 3 randomized controlled trials of frequent HD^{50,57,59}. There are several limitations that should be emphasized. Due to the paucity of randomized controlled trials, this systematic review primarily evaluated observational studies. With the use of single-arm studies, a regression-toward-the-mean phenomenon is a concern, especially because serial M-mode echocardiographic estimates of LVM in healthy volunteers have been associated with substantial variability⁷⁹. In addition, an observation bias introduced by the use of blinded vs. non-blinded readers of the cardiac imaging studies is another source of heterogeneity. Despite these important limitations, the 31.2 g/m² reduction in the mean LVMI represents a 20% improvement over the baseline measurement, paralleling the observed decrease in blood pressure values and the reduction in the number of anti-hypertensive medications. This position is bolstered substantially by the fact that the net reduction in the LVMI averaged 7.0 g/m² (or 8.8%) in the 3 randomized controlled trials that used rigorous and blinded techniques to assess the cardiac chambers. This value compares favorably with a 6-month LVMI decline of 4.9, 4.8, and 5.8 g/m² observed in hypertensive patients with LVH who were treated with aliskiren, losartan, or both, respectively⁸⁰. Our analysis was unable to differentiate between the various types of LV geometry, as LVH can be divided into concentric, eccentric, asymmetric types, and whether the papillary muscle mass was included or excluded from LV chamber measurements. If not reported, the height was imputed using published data on the study country's dialysis population mean height, which might have influenced in change in LVMI. Finally, we were unable to address the potential risks associated with frequent HD, mainly vascular access-related events and cause-specific hospitalizations.

In conclusion, conversion from conventional HD to frequent or extended HD is associated with an improvement in cardiac morphology, cardiac function, and blood pressure parameters. These changes might confer a long-term cardiovascular benefit, calling for the design of large randomized controlled trials of these alternative dialysis regimens with long-term follow up, and aimed at examining cardiovascular morbidity and mortality in this high-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Study selection flow diagram.

Figure 2.

Forest plot displaying the effect of frequent or extended hemodialysis on change in the left ventricular mass index (LVMI). $P < 0.001$; I^2 index = 84% *The study by Chan et al reported 2 studies in the same years whereas Fagugli et al and Weinreich et al included 2 different HD prescriptions in the same study.

Figure 3.

Univariate meta-regression analyses displaying the effect of frequent or extended hemodialysis on change in the left ventricular mass index (LVMI) stratified by duration of follow-up periods (3A), reader variability (3B), and cardiac imaging acquisition technique (3C). Where indicated, P values refer to the univariable meta-regression comparing studies of M-mode echocardiography vs. cardiac MRI († P = 0.009), unspecified mode echocardiography vs. cardiac MRI (‡ P < 0.001), and blinded vs. non-blinded readers (* P = 0.005).

Figure 4.

Univariate meta-regression analyses displaying the effect of frequent of extended hemodialysis on change in the systolic blood pressure (SBP) stratified by the study measurement periods (4A), the mean number of anti-hypertensive medications (4B), and the blood pressure recording technique (4C).

Table 1

Characteristics of the studies included in the meta-analysis

Author	Year	Country	Study design	Study quality*	Sample size	Mean duration of dialysis (mo)	Mean age (y)	Men (%)	HTN (%)	Duration of follow up (mo)	Frequent or extended HD prescription parameters	
											Weekly frequency (d)	Session duration (h)
Buoncristiani	1988	IT	PCS	5	12	NR	NR	NR	NR	27	3.5	1.50
Buoncristiani	1996	IT	RCS	4	34	NR	57	65	59	24	6.5	1.75
Traeger	1998	FR	PCS	5	4	156	51	100	50	12	6.0	2.25
Kooistra	1998	NL	PCS	5	13	116	50	77	NR	6	6.0	2.00
Fagugli	1998	IT	RCS	4	23	49	52	70	65	12	6.5	1.75
Pierratos	1998	CA	PCS	5	12	99.5	40	75	83	34	6.5	9.00
Laurent	1998	FR	RCS	3	103	NR	NR	NR	53	12	3.0	8.00
Williams	1999	US	PCS	4	5	45	55	100	80	2	6.0	8.00
Williams	1999	US	PCS	4	5	29	47	60	60	2	6.0	1.25
Pinciaroli	1999	IT	RCS	4	22	46	52	46	55	66	6.5	1.75
Wood	1999	US	RCS	4	72	24	47	74	46	12	6.0	1.50
Cacho	2000	US	PCS	5	6	NR	NR	NR	NR	6	5.0	7.00
Lindsay	2001	CA	PCS	5	9	NR	45	60	70	12	6.5	2.00
Lindsay	2001	CA	PCS	5	10	NR	43	70	60	6	6.0	7.00
Galland	2001	FR	PCS	5	10	121	45	NR	50	23	6.0	2.25
Fagugli	2001	IT	RXOT	7	12	41	64	33	100	6	6.0	2.00
Traeger	2001	FR	PCS	5	15	139	45	87	100	23	6.0	2.25
McGregor	2001	NZ	RXOT	7	9	25	48	44	NR	2	3.0	7.00
Andre	2002	BR	PCS	5	5	50	41	100	80	24	6.0	2.00
Chan	2002	CA	PCS	5	6	NR	50	NR	33	38	6.0	9.00
Chan	2002	CA	PCS	5	28	NR	44	NR	NR	41	7.0	9.00
Nesrallah	2003	CA	PCS	5	11	NR	45	64	73	18	5.5	2.00
Nesrallah	2003	CA	PCS	5	12	NR	44	83	67	18	5.5	7.00
Koshikawa	2003	JP	NRXOS	6	23	133	56	61	48	3	6.0	2.00
Ting	2003	US	PCS	5	42	78	60	67	91	72	6.0	2.00
Haag-Weber	2003	DE	PCS	5	9	NR	NR	NR	NR	6	3.0	8.00

Author	Year	Country	Study design	Study quality*	Sample size	Mean duration of dialysis (mo)	Men (%)	HTN (%)	Duration of follow up (mo)	Frequent or extended HD prescription parameters	
										Weekly frequency (d)	Session duration (h)
Reynolds	2004	US	PCS	5	15	42	60	53	12	6.0	2.00
Lockridge	2004	US	RCS	4	40	26	50	50	60	5.5	8.00
Traeger	2004	FR	PCS	5	17	11.5	46	53	72	6.0	2.25
Williams	2004	US	PCS	4	20	75	57	80	1	6.0	2.00
Okada	2005	JP	NRXOS	6	6	58	64	50	3	6.0	2.00
Ayus	2005	US	PCS	5	26	34	51	65	12	6.0	3.00
Weinreich	2006	DE	PCS	5	8	59	67	75	12	6.0	2.75
Weinreich	2006	DE	PCS	5	17	94	47	71	12	3.0	7.75
Odor-Cederlof	2006	SE	PCS	4	12	75	55	92	1	6.0	2.00
Fagugli	2006	IT	PCS	5	12	30	58	33	6	6.0	2.00
Fagugli	2006	IT	PCS	5	12	30	59	42	6	3.0	4.75
Goldfarb-Rumyantzev	2006	US	NRXOS	5	12	26	52	50	2	6.0	2.00
He	2006	CN	PCS	4	16	4	67	75	2	6.0	2.00
Zilch	2007	NL	PCS	5	11	127	46	82	6	6.0	2.00
Kraus	2007	US	PCS	4	32	NR	51	63	2	6.0	2.80
Culleton	2007	CA	RCT	8 (3)	26	66	55	69	6	5.5	6.00
Culleton	2007	CA	RCT	8 (3)	25	58	53	56	6	3.0	4.00
Chan	2008	CA	PCS	4	20	NR	41	65	2	6.0	9.00
Bergman	2008	CA	PCS	5	32	108	43	60	24	5.5	9.00
Cravedi	2009	IT	RCS	4	7	172	50	86	24	3.0	8.00
Bugeja	2009	CA	RCS	4	39	38	NR	67	12	3.0	7.50
David	2009	DE	PCS	5	13	59	35	85	12	3.0	8.00
Rayment	2010	AU	PCS	5	6	39	48	100	6	6.0	2.25
Chertow	2010	US	RCT	8 (3)	125	NR	49	62	12	6.0	2.50
Chertow	2010	US	RCT	8 (3)	120	NR	52	61	12	3.0	4.00
Ok	2011	TR	PCS	5	247	61	45	68	12	3.0	8.00
Rocco	2011	US	RCT	8 (3)	45	3.5**	52	64	12	6.0	6.00
Rocco	2011	US	RCT	8 (3)	42	3.5**	54	67	12	3.0	<5.00

AU, Australia; BR, Brazil; CA, Canada; CN, China; DE, Germany; FR, France; IT, Italy; JP, Japan; NL, Netherlands; NZ, New Zealand; SE, Sweden; TR, Turkey; PCS denotes prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled trial; NRXOS, nonrandomized crossover study; RXOT, randomized crossover trial; US, United States; HD, hemodialysis; HTN, hypertension; NR, not reported.

** Median duration of dialysis in both groups.

* Study quality of the cohorts or study arms was assessed by the Newcastle-Ottawa Scale. Where indicated, the parentheses display the Jadad score of the randomized controlled trials.

Summary effect of frequent or extended hemodialysis on cardiac morphology and function, and blood pressure parameters

Table 2

Outcome variables	No. studies	No. participants	Baseline mean value (95% CI)	Mean change* (95% CI)	P value	Assessment of heterogeneity	
						I ² † index	Chi-square P-value
Cardiac morphology and function							
LVM (g)	13	335	238.8 (197.9, 279.7)	-60.5 (-90.8, -30.2)	<0.001	95%	<0.001
LVMi (g/m ²)	23	524	155.7 (109.4, 135.2)	-31.2 (-39.8, -22.5)	<0.001	84%	<0.001
LV systolic diameter (mm)	5	173	37.5 (33.9, 41.0)	-4.3 (-6.8, -1.7)	0.001	69%	0.01
LV end diastolic diameter (mm)	14	314	53.7 (50.7, 56.7)	-4.7 (-6.0, -3.5)	<0.001	55%	0.007
LV posterior wall thickness (mm)	12	213	11.0 (10.5, 11.6)	-1.1 (-1.5, -0.7)	<0.001	61%	0.003
Intraventricular septum thickness (mm)	11	196	12.3 (11.6, 13.1)	-1.6 (-2.1, -1.2)	<0.001	43%	0.06
Left atrial end diastolic diameter (mm)	3	62	40.7 (38.0, 43.4)	-5.2 (-6.0, -4.3)	<0.001	0%	0.48
LVEF (%)	4	137	45.1 (28.1, 62.1)	6.7 (1.6, 11.9)	0.011	74%	0.009
Blood pressure parameters							
SBP (mmHg)	35	928	147.7 (143.7, 151.7)	-14.1 (-17.2, -11.0)	<0.001	89%	<0.001
DBP (mmHg)	31	733	84.1 (81.3, 86.9)	-7.1 (-9.2, -4.9)	<0.001	89%	<0.001
MAP (mmHg)	20	352	110.2 (106.2, 114.1)	-11.8 (-13.8, -9.8)	<0.001	75%	<0.001
No. anti-hypertensive medications	25	552	1.8 (1.6, 2.1)	-0.8 (-1.2, -0.5)	<0.001	97%	<0.001

* by random effects model meta-analysis

† A measure of statistical heterogeneity across study results an I² index 50% indicates medium-to-high heterogeneity¹³.

Abbreviations: LVM, left ventricular mass; LVMi, left ventricular mass index; LV, left ventricular; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CI, confidence interval.