Clinical Kidney Journal, 2025, vol. 18, no. 1, sfae352

https://doi.org/10.1093/ckj/sfae352
Advance Access Publication Date: 14 December 2024
Original Article

ORIGINAL ARTICLE

Effect of intradialytic exercise training on hemodialysis-induced myocardial stunning: a pilot-controlled trial

Matthieu Josse[1], Laure Patrier[2,3], Jean-Paul Cristol[2,4,5], Myriam Isnard[6], Antoine Grandperrin[1], Cécile Turc-Baron[2,4], Stéphane Nottin[1], Stéphane Mandigout[7], Claire Maufrais[1,*] and Philippe Obert[1,*]

[1]UPR_{4278} Laboratory of Experimental Cardiovascular Physiology, Avignon University, Avignon, France, [2]Fondation Charles Mion – AIDER Santé, France, [3]CHU Nîmes, France, [4]CHRU, Montpellier, France, [5]UMR_{9214} PhyMedExp, University of Montpellier, INSERM, CNRS, Montpellier, France, [6]ATIR Avignon, France and [7]HAVAE UPR_{20217}, University of Limoges, F-87000 Limoges, France

*Both senior co-authors and co-corresponding authors.
Correspondence to: Philippe Obert; E-mail: philippe.obert@univ-avignon.fr, Claire Maufrais; E-mail: claire.maufrais@univ-avignon.fr

Watch the video abstract of this contribution

ABSTRACT

Background. Hemodialysis (HD) can lead to left ventricular (LV) transient regional wall motion abnormalities (RWMAs), due to segmental hypoperfusion, better known as myocardial stunning. Repeated episodes of HD-induced ischemia contribute directly to the development of heart failure and increased mortality in patients receiving HD. Intradialytic exercise (IDE) training is capable of exerting favorable effects on the cardiovascular system. However, its impact on HD-induced myocardial stunning remains currently unknown.

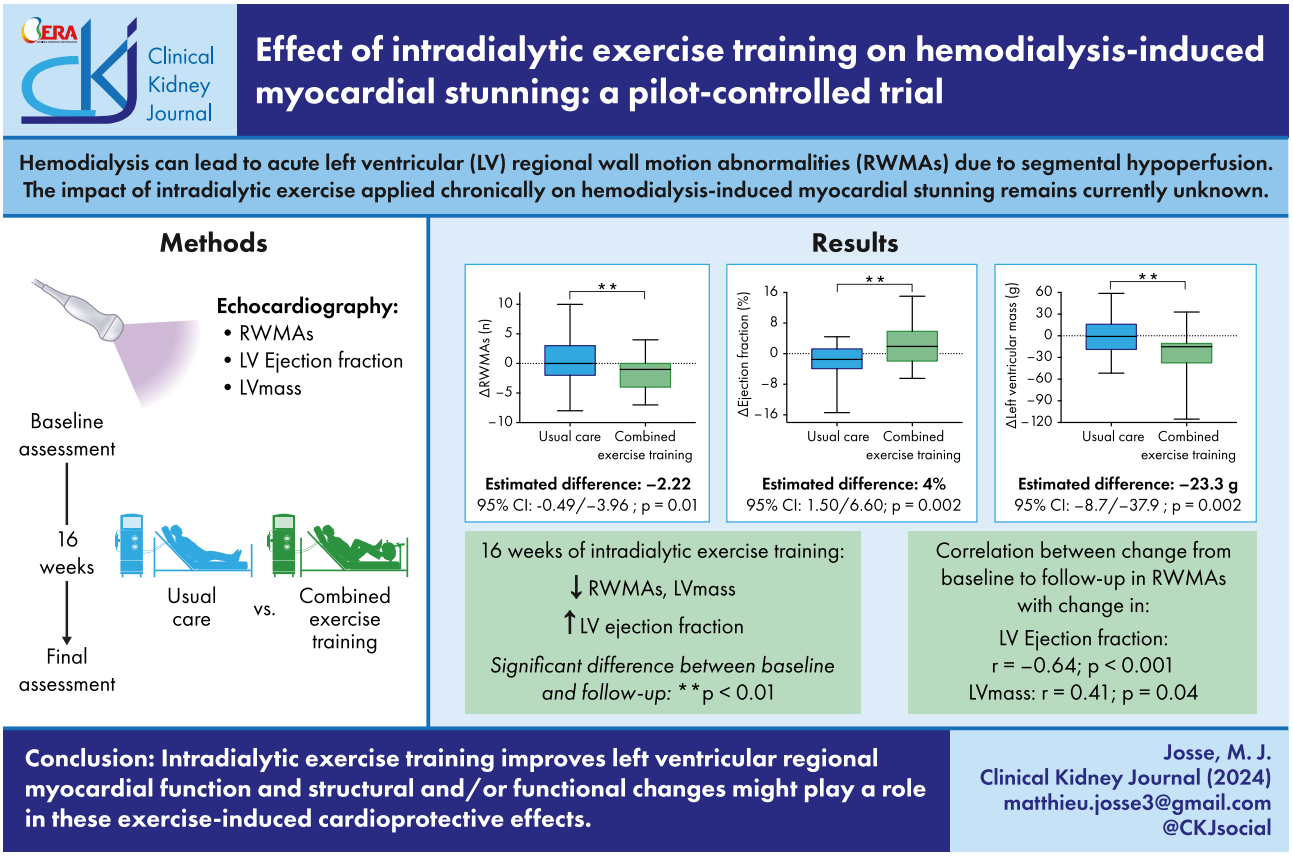
Methods. In this prospective controlled study, 31 patients participating in an intradialytic aerobic and resistance training program (3/week for 16 weeks) were compared with 30 patients receiving usual care. Two-dimensional echocardiography was performed at baseline and follow-up both just before HD onset (T_0) and at peak stress of HD (T_{peak}). LV longitudinal strain from an 18-segment model were used to assess the presence of RWMAs.

Results. Training resulted in a significant reduction of RWMAs at T_{peak} between groups [–2.22 segments; 95% confidence interval (CI) –0.49/–3.96; $P = .01$]. Compared with usual care, trained patients demonstrated also a greater reduction in the decline of global longitudinal strain during HD (–1.45%; 95% CI –0.24/–2.66; $P = .01$). There were significant reductions in LV mass (–23.3 g; 95% CI –8.7/–37.9; $P = .002$) and improvements in LV ejection fraction (4%; 95% CI 1.5/6.6; $P = .002$) between groups favoring IDE. Correlations were found between change in RWMAs with change in LV mass and ejection fraction over the study period.

Conclusion. IDE training is cardioprotective, improving LV remodeling and reducing HD-induced myocardial stunning.

Received: 15.3.2024; Editorial decision: 14.10.2024

GRAPHICAL ABSTRACT



Keywords: cardiovascular disease, echocardiography, hemodialysis

KEY LEARNING POINTS

What was known:

- Hemodialysis (HD) can lead to acute regional wall motion abnormalities due to segmental hypoperfusion.
- Acute intradialytic exercise (IDE) is cardioprotective, reducing the number of stunned segments.
- The impact of IDE applied chronically on HD-induced myocardial stunning remains currently unknown.

This study adds:

- This paper highlights the potential of IDE training as a non-pharmacological intervention to limit myocardial stunning and improve segmental LV myocardial function during HD in people receiving HD.

Potential impact:

- IDE training may contribute to reducing the risk of major cardiac events and mortality associated with recurrent transient LV dysfunction imposed by repetitive HD.
- This study encourages exercise implementation to prevent overt cardiac dysfunction in ESKD patients.

INTRODUCTION

Patients with end-stage kidney disease (ESKD) undergoing maintenance hemodialysis (HD) have high rates of cardiovascular disease and mortality [1, 2], which is not only due to a higher prevalence of traditional risks factors or ESKD-related features but may also be related the HD procedure itself. The rapid fluid and electrolyte shifts during HD lead indeed to hemodynamic instability and acute reduction in left ventricular (LV) myocardial perfusion, resulting in LV regional wall motion abnormalities (RWMAs) [3, 4]. The resultant transient post-ischemic myocardial dysfunction, better known as myocardial stunning [5], has important clinical significance since its prevalence is clearly associated with an increased risk of heart failure or cardiovascular mortality in patients with ESKD [6].

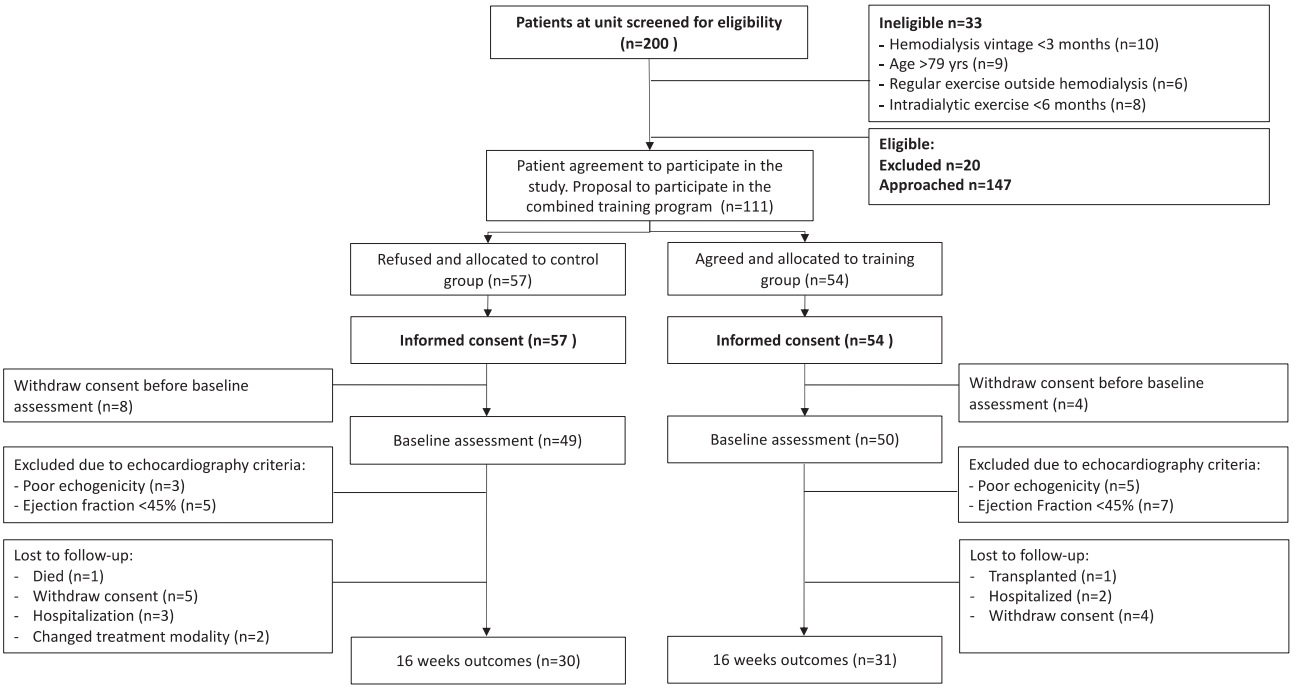


Figure 1: Study consort diagram. Study screening, assigned group, echo window, participation and dropout.

Countermeasure strategies to limit RWMAs during HD procedure are therefore mandatory. Intradialytic exercise (IDE) has emerged in recent years as an attractive non-drug therapeutic strategy for improving cardiovascular health, and is now recommended for patients receiving HD [7, 8]. Chronic IDE training is associated with favorable effects on central hemodynamics, blood pressure (BP) and intradialytic hypotension (IDH) [9]. Acute application of IDE is cardioprotective, reducing myocardial stunning compared with standard HD [10, 11]. Our team has also recently demonstrated its beneficial effects on both LV longitudinal and circumferential deformations and on torsional mechanics [12]. The impact of an IDE training intervention on regional myocardial mechanics and RWMAs during HD is currently unknown. Of note, Graham *et al.* showed that 6 months of intradialytic cycling reduced LV mass, a predisposing factor for myocardial stunning [13, 14]. Our study aims accordingly to explore the impact of a 16-week IDE program on RWMAs and LV myocardial mechanics during a standard HD in patients with ESKD.

MATERIALS AND METHODS

Study design and participants

The EX-CHRODIAL (Chronic Intradialytic Exercise: a Cardioprotective Role) study is a prospective, non-randomized, open-label, parallel and proof-of-concept clinical trial. Patients were recruited from two dialysis centers. Untrained patients, aged 20–79 years, undertaking maintenance HD for >3 months were eligible. Exclusion criteria were contraindication to exercise, ejection fraction (EF) <45%, severe heart or respiratory diseases, severe obesity. All participants signed written informed consent prior enrollment. The study was approved by the ethics committee EastII and registered at ClinicalTrials.gov (NCT04697459). Recruitment began in December 2020 and the study was completed in June 2022.

Treatment allocation and blinding

All patients were offered to participate in a 16-week IDE program. Each patient was given the choice of whether or not to attend this program and was then assigned to one of the two study arms: training group (ENT) or usual care (CTRL). Figure 1 shows the flow chart of patient recruitment. In the absence of randomization, the ROBINS-1 tool was employed for the purpose of measuring the risk of bias [15]. Clinical routine examinations were performed by non-study medical staff. Echocardiographic scans were conducted by experienced sonographers and analyzed off-line by a blinded assessor (M.J.) unaware of patient identity, group allocation or examination order. Thus, outcome assessors were considered blinded.

Interventions

Patients in the ENT group underwent a 16-week combined aerobic and resistance exercise program, with 3 weekly sessions of IDE, in accordance with recommendations [16]. Each session consisted of 30 min of moderate-intensity cycling (Borg scale 12–14 [17]) followed by 30 min of resistance exercises. Exercise was done in a semi-recumbent position on a calibrated cycle ergometer (Oxycycle 3–Physiomed) attached to the patient's bed, starting 30 min after HD onset, including a 5-min warm-up and cool-down at 50% workload. Resistance exercises included knee flexion, leg press, unilateral knee extension, hip flexion, unilateral hip adduction/abduction and calf raise. Knee curl and leg press utilized elastic bands (5–30 kg), while other exercises used ankle weights (1–6 kg). Patients performed two to three sets of 10–15 repetitions at 60%–75% of one repetition maximum. Experienced therapists supervised each session. The training workload was adjusted weekly in order to maintain patients' perceived exertion. The CTRL patients received usual care and were encouraged to maintain their lifestyle.

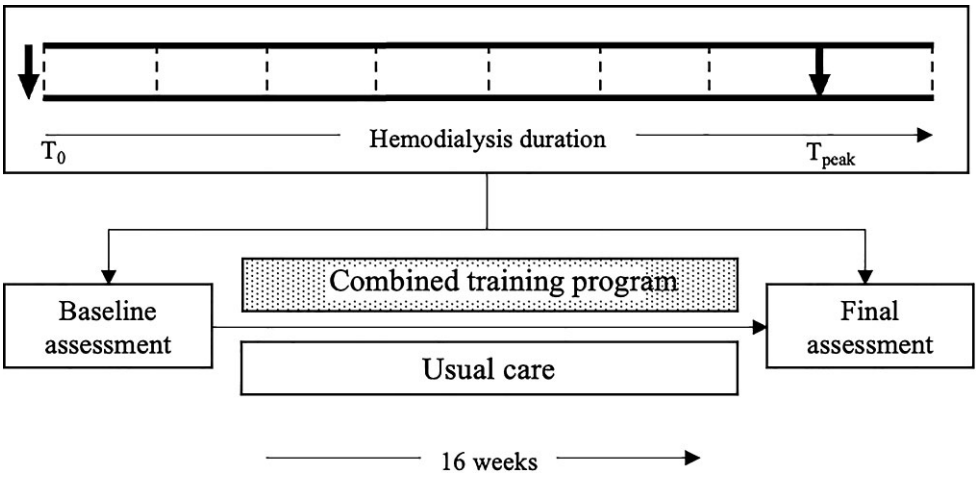


Figure 2: Diagram of the baseline and final assessment of the combined training and the usual care group. Dotted line (⋮) indicates blood pressure and cardiac output measurements. Arrows (↓) indicate transthoracic echocardiography.

Outcome measures

The primary endpoint was group comparison of change from baseline to follow-up in RWMAs during HD. Secondary endpoints included 16-week changes in global longitudinal strain (GLS), central hemodynamics and IDH recorded during HD. Other outcomes included changes in global LV EF and LV remodeling [LV mass, LV end-diastolic volume (EDV) and end-systolic volume], standard biological, clinical and HD parameters as well as biomarkers of myocardial injury. Changes in physical fitness were obtained only in the ENT group.

Echocardiography

Transthoracic echocardiography was performed using a Vivid Q system (3.4-MHz Transducer, GE Healthcare, Norway). Ultrasound scans were obtained just before HD onset (T_0) and at peak stress of HD (i.e. 30 min before HD-ending, T_{peak}) (Fig. 2). Standard parasternal long axis and apical chamber views were recorded for blinded offline analysis using dedicated software (EchoPAC 203TM, GE Healthcare, USA). GLS was measured using speckle-tracking echocardiography (STE) and calculated from an 18-segment model (apical 4, 2 and 3 chamber views), as previously described [12]. RWMAs were identified from the 18-segment model. For each segment, a reduction >20% in peak longitudinal strain at T_{peak} relative to its peak value at T_0 was an indication of RWMA [18]. Systolic meridional wall stress (σ_{es}) and EDV were used as cardiac afterload and preload indexes, respectively [19]. For more details on conventional echocardiographic parameters, see Supplementary data.

Hemodynamics

Monitoring of cardiovascular hemodynamics was set up with measurements staggered every 30 min from HD onset for aortic blood flow, heart rate and BP. Cardiac output (CO) and stroke volume (SV) were measured as previously described [12]. Brachial BP was measured on the non-access arm using an automated blood pressure cuff. IDH was defined as fall of systolic BP of >20 mmHg and/or 10 mmHg of mean arterial pressure from the initial BP at T_0, associated with symptoms [20].

Clinical information

Dialysis information, routine treatment and chemistries were obtained from patient's charts (Tables 1 and 2). Cardiovascular and inflammatory biomarkers were analyzed at T_0 (Supplementary methods). Net ultrafiltration (UF) was determined clinically based on ideal dry weight. Physical function tests [6-min walking test (6MWT) [21] and Short Physical Performance Battery (SPPB) [22]] and adherence to the exercise-training program are detailed in Supplementary materials.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 26.0 (IBM, NY, USA). Continuous data were expressed as mean ± standard deviation, median or lower/upper quartiles and categorical data with frequency count. Statistical significance was defined as a *P*-value <.05. No prior studies investigated the impact of IDE training on RWMAs during HD. Sample size calculation was derived from a myocardial infarction study where 12 weeks of exercise training resulted in a 0.4 difference in RWMA between intervention and control groups [23]. Given a standard deviation of 0.5 in each group, a sample size of 52 participants would be required, with 80% power and a significance level of 5% (G-Power3.1.9.2, Germany). Further, inflating this for an estimated drop-out rate of 10%, we calculated an overall sample size as 58. The primary outcome was analyzed using a generalized linear mixed model (Poisson regression model) with change in the number of RWMAs from baseline to follow-up as the outcome, and time, treatment status and study site as fixed effects and a random effect for patients. There was no missing data at the final visit for the primary outcome. Between-group changes in IDH were assessed with the same statistical model. Secondary outcomes were analyzed using a linear mixed-effects regression model, with change in variable as the dependent variable and treatment status, study site and baseline values (if applicable) as fixed effects and a random effect for patients. For both primary and secondary outcomes, a generalized linear model was used to compare ENT with CTRL at baseline at T_0, and data with significant group differences were used as covariates in the mixed effect models. We used intention-to-treat analyses for all outcomes. A further post-hoc analysis used

Table 1: Baseline participant characteristics.

	CTRL ($n = 30$)	ENT ($n = 31$)	P-value
Age (years)	66 ± 14	64 ± 12	.52
Male sex	25 (81)	21 (68)	.39
Dry weight (kg)	73.8 ± 2.6	69.7 ± 2.6	.28
Body mass index (kg/m^2)	25.6 ± 4.1	24.4 ± 4.7	.26
Dialysis vintage (months)	48 (23–72)	42 (23–97.5)	.85
Comorbidities, *n* (%)			
Diabetes	9 (29)	1 (3)	.01
Hypertension	21 (68)	21 (68)	
Coronary artery disease	3 (10)	1 (3)	.61
Heart failure	5 (16)	5 (16)	
Chronic kidney disease etiology, *n* (%)			
Glomerular nephritis	5 (16)	8 (26)	.54
Immunoglobulin A nephropathy	0 (0)	2 (6)	.49
Hypertensive nephropathy	7 (23)	4 (13)	.50
Diabetic nephropathy	5 (16)	1 (3)	.19
Congenital	1 (3)	2 (6)	.99
Indeterminate	3 (10)	3 (10)	
Others	10 (32)	13 (42)	.60
Medication, *n* (%)			
Antiplatelet	0 (0)	1 (3)	.48
Anticoagulants	11 (35)	6 (19)	.26
ACEi/ARB	5 (16)	0 (0)	.02
Nitrates	0 (0)	0 (0)	
Statins	12 (39)	6 (19)	.17
Diuretics	9 (29)	10 (32)	.79
Anti-arrhythmic	1 (3)	0 (0)	.99
Calcium channel blockers	10 (32)	13 (42)	.60
β-blockers	7 (23)	7 (23)	
Erythropoietin	1 (3)	1 (3)	
Corticosteroids	0 (0)	2 (6)	.22
Thyroxine	1 (3)	0 (0)	.99

Data are given as mean ± standard deviation, *n* (%), or median (lower quartile–upper quartile).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

the Pearson correlation to assess possible relationships between change in RWMAs and physical fitness, IDH episodes and secondary cardiovascular outcomes in the ENT group. Chi-square test was used for group comparison of categorical data.

RESULTS

Baseline characteristics

Between January 2020 and December 2021, 200 patients were screened, of whom 54 agreed to take part in the IDE program and 57 refused and continued with usual care (Fig. 1). After baseline assessments, 12 individuals in ENT and 8 in CTRL were excluded due to poor echogenicity or LV EF <45%. Seven participants in ENT and 11 in CTRL were lost to follow-up, leaving a sample of $n = 31$ for ENT and $n = 30$ for CTRL at the 16-week time-point. Baseline characteristics, comorbidities except diabetes, and prescribed medication were similar between ENT and CTRL. Furthermore, there were also no differences between ENT and CTRL regarding HD vintage, dry weight and ESKD etiology. The risk of bias was assessed across all domains and was evaluated as "low" [15].

Primary outcome

RWMAs were similar at baseline in ENT compared with CTRL ($P = .87$). There was evidence that IDE program resulted in a significant reduction in RWMAs between groups (estimated difference: –2.22 segments; 95% CI –0.49/–3.96; $P = .01$) (Table 3). Change in RWMAs was significant for ENT ($P = .007$) but not CTRL ($P = .31$). No effect of study site was noticed ($P = .91$).

Secondary outcomes

These outcomes are presented in Table 3. There was also evidence that IDE training significantly attenuated the decline in GLS during HD (estimated difference: –1.45%; 95% CI –0.24/–2.66; $P = .01$). There were, however, no between group differences regarding the change in the evolution during HD in loading condition indices (delta EDV: $P = .21$ and delta σ_{es}: $P = .82$). IDE training resulted in a reduction of LV mass between groups (estimated difference –23.3 g; 95% CI –8.7/–37.9; $P = .002$). It yielded also to an increase in EF compared with usual care (estimated difference: 4%; 95% CI 1.5/6.6; $P = .002$). SV and CO gradually declined during all HD sessions in both groups ($P < .01$). Compared with baseline, they were both shifted upwards at 16 weeks in ENT ($P < .001$) while no changes were noticed in CTRL (SV: $P = .82$; CO: $P = .10$) (Fig. 3). Irrespective of time period or groups, BP did not change during HD. There was a non-significant decrease in IDH episodes in ENT compared with CTRL. UF volume was reduced after IDE training (between group difference: $P = .03$, ENT: $P = .002$; CTRL: $P = .96$). There was a group by time by pre-dialysis weight interaction ($P < .001$) and when *post hoc* tests were performed on separate groups, there was no longer a time effect ($P = .53$) from the mixed-effects model with pre-dialysis weight as a covariate

Table 2: Hemodialysis, biological, biomarkers and physical function test at baseline and 16 weeks by groups arms.

	CTRL			ENT			
	Baseline	16 weeks	P-value[a]	Baseline	16 weeks	P-value[a]	P-value[b]
HD parameters							
Weight (kg)							
Pre	76.2 ± 14.2	76.5 ± 14.5	.53	72.2 ± 16.0	71.3 ± 16.1	.90	.67
Post	73.6 ± 13.7	74.2 ± 14.1	.91	69.7 ± 15.7	69.2 ± 15.6	.46	.56
UF volume (L)	2.35 ± 0.80	2.40 ± 1.09	.96	2.51 ± 1.10	2.05 ± 1.02	**.002**	**.03**
Duration (min)	231 ± 20	234 ± 18	.10	224 ± 19	223 ± 18	.94	.29
UF rate (mL/h)	685 ± 212	705 ± 229	.72	684 ± 208	588 ± 217	.08	.10
Kt/V	1.59 ± 0.23	1.58 ± 0.27	.43	1.51 ± 0.22	1.48 ± 0.28	.12	.11
Biologic parameters							
Hemoglobin (g/100 mL)	11.0 ± 1.1	11.3 ± 1.2	.41	11.7 ± 1.3	11.4 ± 1.0	.12	.09
Calcium (mmol/L)	2.18 ± 0.12	2.25 ± 0.14	**.01**	2.20 ± 0.17	2.27 ± 0.17	.04	.96
Potassium (mmol/L)	4.87 ± 0.70	4.74 ± 0.67	.52	5.04 ± 0.74	4.85 ± 0.88	.19	.66
Sodium (mmol/L)	138.8 ± 3.0	138.0 ± 3.6	.30	138.2 ± 2.6	139.0 ± 2.9	.07	.06
Creatinine (μmol/L)	805 ± 216	737 ± 223	**.02**	755 ± 206	763 ± 225	.70	.12
Urea (mmol/L)	20.4 ± 5.0	18.8 ± 6.0	.14	22.4 ± 5.2	18.8 ± 5.5	**<.001**	.22
Albumin (g/L)	38.7 ± 3.8	39.5 ± 4.2	.52	41.8 ± 5.8	40.4 ± 3.6	.77	.67
Hs-CRP (mg/L)[c]	3.2 (0.8–5.6)	5.0 (0.7–7.8)	**.04**	1.5 (0.7–6.1)	2.7 (1.3–5.9)	**.02**	.33
IL-6 (pg/mL)[c]	5.2 (3.4–8.6)	6.6 (5.3–10.1)	.09	6.9 (3.4–11.6)	6.3 (4.6–10.7)	.83	.28
NT-proBNP (pg/mL)[c]	3606 (1694–7630)	3578 (1832–10 001)	**.04**	2543 (1330–5180)	3440 (1852–5483)	**.02**	.78
CTnI (ng/L)[c]	44.3 (32.3–66.1)	47.0 (27.8–73.6)	.96	50.5 (35.3–74.3)	51.5 (31.2–71.4)	.77	.87
Physical function test							
6MWT (m)				333 ± 110	379 ± 93	**<.001**	
SPPB (score)				10.6 ± 1.7	11.2 ± 1.3	**.007**	

[a]P-value for change (difference between baseline and 16 weeks) within each group analyzed using one-sample t-test.
[b]P-value for the between-group difference in the change from baseline to 16 weeks in secondary outcome, analyzed using the linear mixed-effects regression model.
[c]Data summarized as median (lower quartile–upper quartile); P-values from analysis of log-transformed values.
Hs-CRP, high sensitive C-reactive protein; IL-6, interleukin-6; CTnI, cardiac Troponin-I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; 6MWT, 6-min walking test; SPPB, Short Physical Performance Battery.

Table 3: Between-group changes in primary and secondary cardiovascular outcomes during HD over the study period.

	CTRL			ENT			Between-group	
	Baseline	16 weeks	P-value[a]	Baseline	16 weeks	P-value[a]	difference (95 % CI)	P-value[b]
Primary outcome								
RWMAs	6.1 ± 3.2	6.8 ± 3.8	.31[b]	6.0 ± 3.1	4.5 ± 2.2	.007[b]	–2.22 (–0.49 to –3.96)	.01[b]
Secondary outcomes								
STE and hemodynamics								
Delta GLS[c]	2.0 ± 2.0	2.4 ± 2.3	.32	2.1 ± 2.3	1.0 ± 1.9	.02	–1.45 (–0.24 to –2.66)	.01
Delta EDV[c]	–5.5 ± 21.3	–16.3 ± 19.6	.01	–5.5 ± 20.2	–8.0 ± 19.9	.52	7.5 (–4.2 to 19.2)	.21
Delta σ_{es}[c]	–10.5 ± 41.7	–11.5 ± 29.0	.76	–6.0 ± 36.8	–5.5 ± 43.0	.95	–3.9 (–38.9 to 31.0)	.82
IDH	2.1 ± 2.0	1.9 ± 2.3		1.9 ± 2.1	1.5 ± 1.9		–0.22 (–1.5 to 1.03)	.62[b]
Standard echocardiography[d]								
LV EDV (mL)	113 ± 28	105 ± 28	.01	110 ± 34	120 ± 32	.02	18.9 (8.0 to 29.7)	.001
LV ESV (mL)	57 ± 14	55 ± 15	.20	59 ± 21	61 ± 20	.49	4.6 (–2.4 to 11.6)	.19
LV EF (%)	49 ± 5	48 ± 5	.01	46 ± 8	49 ± 7	.05	4.0 (1.5 to 6.6)	.002
LV mass (g)	169 ± 54	174 ± 56	.94	170 ± 57	145 ± 55	.001	–23.3 (–8.7 to –37.9)	.002

[a]P-value for change (i.e. difference between baseline and 16 weeks) within each group analyzed using one-sample t-test.
[b]P-value of group by time interaction or time effect within each group generated by the generalized linear mixed model (using a Poisson regression model) for RWMAs and IDH and P-value of group effect generated by the linear mixed-effects regression model for the other variables. In each case, usual care was used as reference factor.
[c]Change from T_0 to T_{peak}.
[d]measured at T_{peak}.

for the ENT group. Changes over the study period in other HD parameters, physical fitness and biological parameters or EF and hemodynamic variables assessed at T_0 are described in Supplementary data. There was no effect of study site for all variables.

Correlations of change from baseline to follow-up

Data are reported in Table 4. There were no correlations between change in RWMAs and change in UF volume and rate. When considering variables measured during HD, correlations were

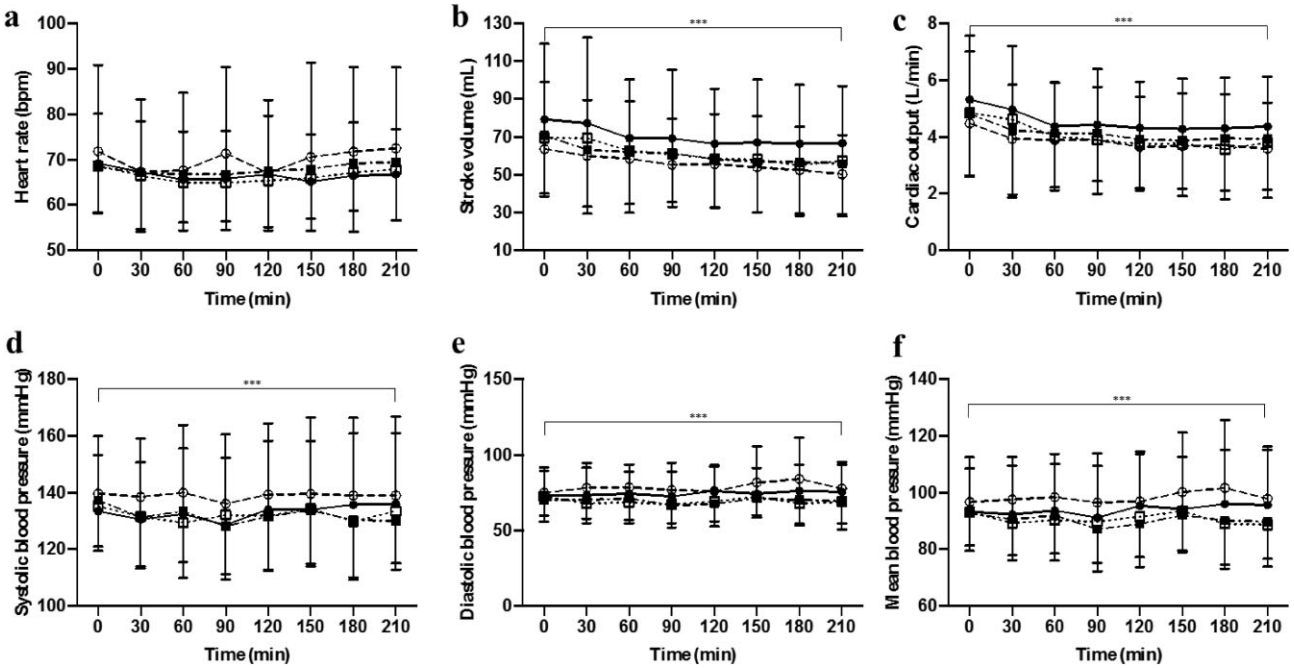


Figure 3: Time course of heart rate (**a**), SV (**b**), CO (**c**), systolic BP (**d**), diastolic BP (**e**) and mean BP (**f**) before and after 16 weeks in two groups (ENTpre °, CTRLpre □, ENTpost ●, CTRLpost ■). ***P < .001, changes from baseline in ENT using a linear mixed-effects model.

Table 4: Correlations between changes in RWMAs over the study period and changes in other outcomes.

Outcomes	Correlation coefficient (r)	*P*-value
UF volume	0.14	.44
UF rate	–0.02	.91
Changes EDV	–0.20	.28
Changes σ_{es}	0.20	.34
LV mass	0.41	.04
EF	–0.64	<.001
Changes SBP	0.15	.41
Changes DBP	0.08	.64
Intradialytic hypotension	–0.21	.26

SBP, systolic blood pressure; DBP, diastolic blood pressure.

noticed between change in RWMAs with change in delta GLS but not delta loading conditions indexes (Table 4). Finally, there were correlations between change in RWMAs and change in LV mass and EF, but not SV, CO, systolic BP, diastolic BP, 6-minutes walking test, SPPB or the number of IDH episodes.

DISCUSSION

Our study aimed to explore the impact of a 16-week IDE program on LV regional myocardial function during HD in ESKD patients. The first striking, yet never demonstrated, finding was the reduction in RWMAs and limitation of GLS decline during HD after IDE training.

STE-derived parameters are good markers of myocardial ischemia and excellent surrogates of intrinsic contractility properties [19, 24]. Our results therefore strongly suggest a favorable impact of IDE training on myocardial perfusion during HD and subsequently on improving regional myocardial function. However, we have to consider that these STE indexes are affected by cardiac loading conditions, which must therefore be taken into account in their interpretation. Volume control is crucial during HD to maintain hemodynamic stability and optimize myocardial function. Most HD characteristics were similar at baseline and follow-up, except UF volume that was significantly reduced in ENT after training (Table 2). This could have limited intravascular volume depletion during HD, thereby increasing myocardial preload. No between-group difference regarding change from baseline to follow-up in delta EDV during HD was noticed however. Similar results were obtained for delta σ_{es}, an index of cardiac afterload (Table 3). Furthermore, changes over the study period in UF volume or evolution of loading conditions during HD were not related to changes in RWMAs in ENT patients (Table 4). Overall, these results argue for mechanisms other than hemodynamics to explain the training-induced reduction in myocardial stunning during HD, most likely involving adaptive changes in myocardial structural and functional remodeling. Impaired perfusion in microcirculatory territories is considered a major factor in HD-induced myocardial ischemia [3, 25]. Regular exercise stimulates the release of growth factors such as vascular endothelial growth factor and fibroblast growth factor, promoting the genesis of new blood vessels, improving capillary network formation and thus increasing coronary collateralization [26]. Exercise training is also recognized for its ability to improve coronary endothelium-dependent vasodilation [27]. These exercise-induced adaptations of the coronary micro- and macro-circulation could contribute to improved myocardial perfusion, oxygen delivery and thus myocardial function, which might explain our findings regarding RWMAs and longitudinal strain kinetics during HD. Using cardiac magnetic resonance imaging, Graham-Brown *et al.* reported a significant reduction in LV mass after 6 months of IDE training [14], in line with our own data. Remarkably, they also noted a simultaneous reduction in LV interstitial myocardial fibrosis, a common phenomenon in ESKD hearts, escalating with maintenance HD duration [28].

Myocardial fibrosis is able to impair myocardial mechanics and contractility [29–31]. Although we were unable to assess myocardial interstitial fibrosis, it is tempting to speculate that its regression may have occurred, potentially explaining the cardioprotection observed in our trial. Supporting this hypothesis is the significant correlation observed between changes following intervention in RWMAs and LV mass in ENT patients (Table 4). Abnormal calcium handling in cardiomyocytes, crucial for regulating contractility, can impair LV strains [32, 33]. Of note, exercise training has been shown to exert beneficial effects on myocardium calcium handling [34]. Whether this also applied to our ESKD patients is unknown, but constitutes a plausible assumption.

Clinical implication

Our results regarding RWMAs and GLS decline during HD after IDE training are clinically relevant. In the general population, RWMAs in at least one segment was associated with a higher risk of incident heart failure (hazard ratio 3.63; $P < .001$) in individuals with successful kidney transplant, the hazards ratio for cardiovascular events or death increased by 28% per 1% decrement in absolute value of GLS [35, 36]. Another clinically significant outcome is the improvement in EF, a traditional marker for cardiovascular mortality and prognosis. Such an improvement might be at least in part be explained by improvements in longitudinal function since change in EF after intervention in ENT correlated well with change in RWMAs ($r = –0.64$; $P < .001$). LV hypertrophy is a common cardiovascular complication in individuals with ESKD [37]. In HD patients, LV hypertrophy is also associated with an increased risk of cardiovascular events and constitutes an independent predictor of poor survival [38], reinforcing the clinical relevant of our own data. By integrating exercise into their HD routine, ESKD patients can potentially benefit from improved LV function, regression of LV hypertrophy and improved overall cardiovascular health. Follow-up clinical and echocardiographic data should be collected over time in large-scale trials to further investigate the effects of intradialytic exercise training on adverse events and mortality.

Study limitation

Our study had several limitations. Even if the trial was powered enough to detect significant reduction in RWMAs after intervention in ENT compared with CTRL, we must recognize its too-small sample size. Large-scale clinical trials will be needed to confirm the results of this proof-of-concept study. Individuals with severe obesity (owing to too poor echogenicity), reduced EF (<45%) and severe heart disease (to minimize any potential cardiovascular risk from exercise) were excluded, affecting the generalizability of our results. The trial recruited only 32% of women; this bias constituted also a limitation regarding gender generalization. Future larger-scale studies, with less restrictive exclusion criteria, will be needed to confirm our results and extend them beyond the actual population. Exercise intensity was based on perceived exertion rather than the results of a previous triangular maximal cardiopulmonary test, avoiding people exercising at strictly the same intensity within the moderate intensity zone expected. The prescription of exercise intensity based on perceived exertion rate is well accepted by people with ESKD and recommended in this population [16]. The drop-out rate from the study was high but equal between groups and similar to other trials [14, 39, 40]. The absence of randomization is a limitation that must be recognized. LV mass was estimated using echocardiography, which is not optimal in the context of HD, considering that parameters of the Devereux's predictive equation are affected by loading conditions. Scanning was carried out at the end of HD to avoid as far as possible the influence of HD-dependent reduction in loading conditions. However, our results fit well with those of Graham-Brown *et al.*, who used cardiac magnetic resonance imaging, the current reference method [14]. We were unable to assess myocardial perfusion and interstitial fibrosis in our study. Future studies using functional cardiac MRI or positron emission tomography are required to provide more precise information about the effect of IDE training on myocardial blood flow and fibrotic tissue as well as their links with improvement in LV regional myocardial function during HD (i.e. RWMAs, GLS decline).

CONCLUSION

Our findings highlight the potential of IDE training as a non-pharmacological intervention to limit myocardial stunning and improve global and segmental myocardial function during HD in individuals with ESKD. This cardioprotection offered by IDE training is of significant clinical importance, as it might prevent overt cardiac dysfunction and reduce the risk of major cardiac events and mortality associated with recurrent transient LV dysfunction imposed by repetitive HD.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

ACKNOWLEDGEMENTS

We thank Axelife and PACA region to support the scholarship of M.J.

FUNDING

This study was supported by the "Société Française de Cardiologie," grant number SFC21EXCRO and the "Fonds de dotation Villa M," grant number VILLAM22EXCRO.

AUTHORS' CONTRIBUTIONS

P.O. and C.M. conceptualized the study, were responsible for the methodology, funding acquisition and wrote the original draft. P.O., C.M., M.I., L.P. and J.-P.C. were responsible for supervision and validation. P.O., C.M., M.I., L.P., C.T.-B., J.-P.C. and S.M. were responsible for resources. M.J., P.O., C.M., A.G. and S.N. were involved in data collection and analysis. M.J., P.O. and C.M. were responsible for formal analysis, writing review, editing and visualization.

DATA AVAILABILITY STATEMENT

Anonymized data have been deposited to Figshare, 10.6084/m9.figshare.24551281. The raw data supporting the conclusions will be made available without undue reservation.

CONFLICT OF INTEREST STATEMENT

None.

REFERENCES

1. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296–305.
2. Cozzolino M, Mangano M, Stucchi A *et al*. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant* 2018;**33**:28–34. https://doi.org/10.1093/ndt/gfy174
3. Buchanan C, Mohammed A, Cox E *et al*. Intradialytic cardiac magnetic resonance imaging to assess cardiovascular responses in a short-term trial of hemodiafiltration and hemodialysis. *J Am Soc Nephrol* 2017;**28**:1269–77. https://doi.org/10.1681/ASN.2016060686
4. Dasselaar JJ, Slart RHJA, Knip M *et al*. Haemodialysis is associated with a pronounced fall in myocardial perfusion. *Nephrol Dial Transplant* 2008;**24**:604–10. https://doi.org/10.1093/ndt/gfn501
5. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982;**66**:1146–9. https://doi.org/10.1161/01.CIR.66.6.1146
6. Burton JO, Jefferies HJ, Selby NM *et al*. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009;**4**:914–20. https://doi.org/10.2215/CJN.03900808
7. Ferrari F, Helal L, Dipp T *et al*. Intradialytic training in patients with end-stage renal disease: a systematic review and meta-analysis of randomized clinical trials assessing the effects of five different training interventions. *J Nephrol* 2020;**33**:251–66. https://doi.org/10.1007/s40620-019-00687-y
8. Young HML, March DS, Graham-Brown MPM *et al*. Effects of intradialytic cycling exercise on exercise capacity, quality of life, physical function and cardiovascular measures in adult haemodialysis patients: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2018;**33**:1436–45. https://doi.org/10.1093/ndt/gfy045
9. Rhee SY, Song JK, Hong SC *et al*. Intradialytic exercise improves physical function and reduces intradialytic hypotension and depression in hemodialysis patients. *Korean J Intern Med* 2019;**34**:588–98. https://doi.org/10.3904/kjim.2017.020
10. McGuire S, Horton EJ, Renshaw D *et al*. Cardiac stunning during haemodialysis: the therapeutic effect of intra-dialytic exercise. *Clin Kidney J* 2019;**14**:1335–44. https://doi.org/10.1093/ckj/sfz159
11. Penny JD, Salerno FR, Brar R *et al*. Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning. *Nephrol Dial Transplant* 2019;**34**:1917–23. https://doi.org/10.1093/ndt/gfy376
12. Josse M, Patrier L, Isnard M *et al*. Cardioprotective effect of acute intradialytic exercise: a comprehensive speckle-tracking echocardiography analysis. *J Am Soc Nephrol* 2023;**34**:1445–55. https://doi.org/10.1681/ASN.0000000000000149
13. Assa S, Hummel YM, Voors AA *et al*. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors, and prognostic significance. *Clin J Am Soc Nephrol* 2012;**7**:1615–23. https://doi.org/10.2215/CJN.00850112
14. Graham-Brown MPM, March DS, Young R *et al*. A randomized controlled trial to investigate the effects of intra-dialytic cycling on left ventricular mass. *Kidney Int* 2021;**99**:1478–86. https://doi.org/10.1016/j.kint.2021.02.027
15. Sterne JA, Hernán MA, Reeves BC *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;i4919. https://doi.org/10.1136/bmj.i4919
16. Baker LA, March DS, Wilkinson TJ *et al*. Clinical practice guideline exercise and lifestyle in chronic kidney disease. *BMC Nephrol* 2022;**23**:75. https://doi.org/10.1186/s12882-021-02618-1
17. Borg G. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;**14**:377–81. https://doi.org/10.1249/00005768-198205000-00012
18. McIntyre CW, Burton JO, Selby NM *et al*. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol* 2008;**3**:19–26. https://doi.org/10.2215/CJN.03170707
19. Amundsen BH, Helle-Valle T, Edvardsen T *et al*. Noninvasive myocardial strain measurement by speckle tracking echocardiography. *J Am Coll Cardiol* 2006;**47**:5. https://doi.org/10.1016/j.jacc.2005.10.040
20. Kanbay M, Ertuglu LA, Afsar B *et al*. An update review of intradialytic hypotension: concept, risk factors, clinical implications and management. *Clin Kidney J* 2020;**13**:981–93. https://doi.org/10.1093/ckj/sfaa078
21. Segura-Ortí E, Martínez-Olmos FJ. Test-retest reliability and minimal detectable change scores for sit-to-stand-to-sit tests, the six-minute walk test, the one-leg heel-rise test, and handgrip strength in people undergoing hemodialysis. *Phys Ther* 2011;**91**:1244–52. https://doi.org/10.2522/ptj.20100141
22. Cohen B, Munugoti S, Kotwani S *et al*. Continuous long-term physical activity monitoring in hemodialysis patients. *Kidney360* 2022;**3**:1545–55. https://doi.org/10.34067/KID.0002082022
23. Elshazly A, Hasan RL, Saleh MA *et al*. Impact of exercise training on myocardial contractile functions assessed by cardiac magnetic resonance in post-myocardial infarction patients. *Egypt Heart J* 2022;**74**:51. https://doi.org/10.1186/s43044-022-00288-4
24. Jamal F, Strotmann J, Weidemann F *et al*. Noninvasive quantification of the contractile reserve of stunned myocardium by ultrasonic strain rate and strain. *Circulation* 2001;**104**:1059–65. https://doi.org/10.1161/hc3501.093818
25. Selby NM, McIntyre CW. The acute cardiac effects of dialysis: acute cardiac effects of dialysis. *Semin Dial* 2007;**20**:220–8. https://doi.org/10.1111/j.1525-139X.2007.00281.x
26. Fiuza-Luces C, Santos-Lozano A, Joyner M *et al*. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. *Nat Rev Cardiol* 2018;**15**:731–43. https://doi.org/10.1038/s41569-018-0065-1
27. Hambrecht R, Wolf A, Gielen S *et al*. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med* 2000;**342**:454–60. https://doi.org/10.1056/NEJM200002173420702
28. Gross ML, Ritz E. Hypertrophy and fibrosis in the cardiomyopathy of uremia-beyond coronary heart disease. *Semin Dial* 2008;**21**:308–18. https://doi.org/10.1111/j.1525-139X.2008.00454.x
29. Kramann R, Erpenbeck J, Schneider RK *et al*. Speckle tracking echocardiography detects uremic cardiomyopathy early and predicts cardiovascular mortality in ESRD. *J Am Soc Nephrol* 2014;**25**:2351–65. https://doi.org/10.1681/ASN.2013070734
30. Peng Y, Popović ZB, Sopko N *et al*. Speckle tracking echocardiography in the assessment of mouse models of cardiac dysfunction. *Am J Physiol Heart Circ Physiol* 2009;**297**:H811–20. https://doi.org/10.1152/ajpheart.00385.2009
31. Kansal MM, Panse PM, Abe H *et al*. Relationship of contrast-enhanced magnetic resonance imaging-derived intramural

scar distribution and speckle tracking echocardiography-derived left ventricular two-dimensional strains. *Eur Heart J Cardiovasc Imaging* 2012;**13**:152–8. https://doi.org/10.1093/ejechocard/jer163
32. Gorcsan J, Tanaka H. Echocardiographic assessment of myocardial strain. *J Am Coll Cardiol* 2011;**58**:1401–13. https://doi.org/10.1016/j.jacc.2011.06.038
33. Reant P, Labrousse L, Lafitte S *et al*. Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during Dobutamine stress echocardiography in ischemic conditions. *J Am Coll Cardiol* 2008;**51**:149–57. https://doi.org/10.1016/j.jacc.2007.07.088
34. Locatelli J, De Assis LVM, Isoldi MC. Calcium handling proteins: structure, function, and modulation by exercise. *Heart Fail Rev* 2014;**19**:207–25. https://doi.org/10.1007/s10741-013-9373-z
35. Espersen C, Modin D, Platz E *et al*. Global and regional wall motion abnormalities and incident heart failure in the general population. *Int J Cardiol* 2022;**357**:146–51. https://doi.org/10.1016/j.ijcard.2022.03.027
36. Biering-Sorensen T, Biering-Sørensen SR, Olsen FJ *et al*. Global longitudinal strain by echocardiography predicts long term risk of cardiovascular morbidity and mortality in a low risk general population: the Copenhagen City Heart study. *J Am Coll Cardiol* 2016;**67**:1584. https://doi.org/10.1016/S0735-1097(16)31585-6
37. Paoletti E, Bellino D, Cassottana P *et al*. Left ventricular hypertrophy in nondiabetic predialysis CKD. *Am J Kidney Dis* 2005;**46**:320–7. https://doi.org/10.1053/j.ajkd.2005.04.031
38. Zoccali C, Tripepi G, Mallamaci F. Predictors of cardiovascular death in ESRD. *Semin Nephrol* 2005;**25**:358–62. https://doi.org/10.1016/j.semnephrol.2005.05.002
39. Anding K, Bär T, Trojniak-Hennig J *et al*. A structured exercise programme during haemodialysis for patients with chronic kidney disease: clinical benefit and long-term adherence. *BMJ Open* 2015;**5**:e008709. https://doi.org/10.1136/bmjopen-2015-008709
40. Koh KP, Fassett RG, Sharman JE *et al*. Effect of intradialytic versus home-based aerobic exercise training on physical function and vascular parameters in hemodialysis patients: a randomized pilot study. *Am J Kidney Dis* 2010;**55**:88–99. https://doi.org/10.1053/j.ajkd.2009.09.025

Received: 15.3.2024; Editorial decision: 14.10.2024