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# Cardioprotective effect of intradialytic exercise on left atrial mechanics

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## Keywords:

hemodialysis; intradialytic exercise; left atrium; myocardial function.

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## Abstract

Left atrial (LA) function plays a pivotal role in cardiac performance by modulating left ventricular (LV) function. Impairments in LV function are commonly reported during hemodialysis (HD), but available data describing changes in LA function are limited. There is growing evidence of the cardioprotective effect of intradialytic exercise (IDE) on LV function, but studies analyzing its effect on LA function are scarce. Our aim was to evaluate whether IDE can limit the severity of HD-induced impairment in LA myocardial function. In this prospective, open-label, two-center randomized crossover trial, 56 stable individuals receiving HD participated in 2 HD sessions in random order: standard HD and a session incorporating 30 min of aerobic exercise. LA and LV global longitudinal strains (GLSs) were obtained before and at peak stress of HD (i.e., 30 min before the HD ending). IDE totally eradicated the decline in LA reservoir strain observed during HD (estimated difference: 3.1%, 95% confidence interval: 0.4/5.8,  $P = 0.02$ ), whereas it did not affect the other components of LA mechanics. A similar result favoring IDE intervention was also demonstrated on GLS changes over the HD procedure ( $P < 0.001$ ). Between-session differences of changes in GLS and LA reservoir strain were correlated ( $r = -0.32$ ,  $P = 0.03$ ). The cardioprotective effect of IDE disappeared in patients with LA enlargement (i.e., LA volume index  $>34$  mL/m<sup>2</sup>). In conclusion, even a short duration of IDE at moderate intensity is effective in preventing HD-associated decline in LA reservoir function. Further research is needed to explore the long-term benefits of IDE on LA function.

**NEW & NOTEWORTHY** A single bout of intradialytic exercise (IDE) at moderate intensity can prevent the hemodialysis-associated decline in left atrial (LA) function. This was partially explained by the relative preservation of left ventricular systolic function with IDE. Benefits of IDE on LA function were lost in patients with LA dilation. Further studies are needed to explore the mechanisms behind IDE-induced cardioprotection and evaluate the clinical impacts of the repetitive cardioprotective effects of IDE on LA function.

# INTRODUCTION

Chronic kidney disease is a progressive condition that affects >10% of the general population worldwide, amounting to >800 million individuals (1). The prevalence and incidence of end-stage kidney disease (ESKD) requiring dialysis is today increasing, with the majority of patients undertaking hemodialysis (2). In patients with ESKD, mortality is increased by 10- to 20-fold compared with the general population (3). In particular, cardiovascular mortality contributes to 40% of all-cause mortality (4).

Left atrial (LA) enlargement, abnormal left ventricular (LV) geometry and structure (e.g., fibrosis), and global systolic and diastolic dysfunction are well-documented in patients with ESKD (5–9). A myriad of mechanisms including comorbidities (e.g., hypertension, diabetes, and dyslipidemia) and factors related to ESKD itself (e.g., volume overloading, uremia, and inflammation) can lead to these cardiac abnormalities (10). Despite hemodialysis being critical to survival, it is associated with numerous side effects including some cardiac complications (11). Intradialytic hypotension and disturbances in myocardial segmental perfusion (12–14), leading to transient LV dysfunction (14), are well described. The LA function plays a pivotal role in cardiac performance by modulating LV function. LA contributes to LV filling by its reservoir (corresponding to the LV isovolumic contraction, ejection, and isovolumic relaxation), conduit (passage of blood from the LA and pulmonary veins to the LV during passive LV filling), and booster pump (atrial contraction during late diastole encompassing active LV filling) function (15). Although the assessment of LA function can be obtained noninvasively by conventional trans-thoracic two-dimensional (2-D) phasic volumes and Doppler (both spectral and tissue) echocardiography, its detailed quantification remains challenging and time consuming. Evaluation of LA strain derived from 2-D speckle tracking echocardiography is feasible and constitutes a robust approach for assessment of LA mechanics. LA strain describes the deformation of the LA during the cardiac cycle. It can be calculated as the peak systolic change in the segment length relative to the length at the end diastole, and is represented as percentage (%). Compared with the traditional parameters of LA function, strain parameters are relatively independent of tethering effects, less load dependent, and more sensitive to subtle changes in myocardial intrinsic contractility/relaxation properties (16). In addition, strain parameters allow evaluation of phasic atrial function throughout the cardiac cycle. However, there is limited data describing the changes in LA strains during hemodialysis in patients with ESKD (17).

Repetitive episodes of ischemia during hemodialysis can push patients with ESKD to heart failure (18). In this context, the development of strategies to preserve cardiac function during hemodialysis is therefore crucial. Acute physical exercise has the exciting potential to be cardioprotective in patients receiving hemodialysis. Indeed, very recent studies from our laboratory (19) and others (20, 21) reported that intradialytic cycling attenuates the decline in LV strain and decreases the occurrence of LV wall motion abnormalities when compared with

standard hemodialysis. Nevertheless, to the best of our knowledge, the cardioprotective effects of IDE on LA function have never been investigated.

Accordingly, the aim of the present study was to evaluate whether intradialytic exercise (IDE) can have a cardioprotective role, by limiting the severity of hemodialysis-induced impairment in LA function.

## METHODS

### Study Design and Participants

The chronic intradialytic exercise: a cardioprotective role (EX-CHRODIAL) trial was a prospective, open-label, randomized trial incorporating an acute phase (i.e., acute IDE) performed in two hemodialysis units in France. It aimed to investigate the effect of acute IDE on LV and LA myocardial mechanics over the course of hemodialysis. A comprehensive analysis of the LV mechanics has already been published (19), and the present study is focusing on the LA mechanics. The ethics committee East II (clinicaltrials.gov NCT04697459) approved this study. All participants provided written informed consent. Adults, aged 20–79 yr, with no regular exercise outside of dialysis, and no exposure to IDE before the study (<6 mo), undertaking maintenance hemodialysis for >3 mo, were eligible to participate. Exclusion criteria were poor echogenicity, contraindication to exercise, orthopedic complications, severe heart (ischemic, valvular, etc.) vascular or respiratory diseases, ejection fraction (EF) <45%, body mass index >35 kg·m<sup>2</sup>, and pregnancy. Figure 1A shows a flow chart of patient enrollment. Fifty-six patients were included in the final analysis. Participants were assessed under two different conditions: a standard hemodialysis (HD) and a session incorporating 30 min of constant aerobic exercise (HDEX). In this manner, participants served as their own controls. The order of the sessions was randomized via computer. Exercise was performed on a specially adapted calibrated cycle ergometer (OxyCycle 3—PhysioMed) fixed to each patient's bed. The study design is presented in Fig. 1B. During HDEX, the patients performed 30 min of continuous cycling (50–70 rpm) at moderate intensity (11–14 on the 6–20 Borg Rating of Perceived Exertion Scale), as already prescribed in previous studies to evaluate the effects of intradialytic exercise on LV function (20, 21). The intervention started 30 min after hemodialysis onset. Echocardiography was performed twice during each study session: immediately before hemodialysis (T0) and at peak stress of hemodialysis (i.e., 30 min before hemodialysis ending, T<sub>peak</sub>). Blood pressure (BP) and cardiac output were collected at T0 and every 30 min throughout dialysis. For consistency and to avoid the effects of inter-hemodialysis fluid accumulation, HD and HDEX were performed 1 wk apart the same day of the week.

## **Clinical Examination and Dialysis Settings**

Blood samples were collected at T0 (Table 1). All patients were dialyzing three sessions weekly. Treatment times ranged from 4 to 4.5 h. Hemodialysis treatment details are summarized for each session in Table 2.

## **Echocardiography**

### *Data acquisition.*

Transthoracic echocardiography was performed using a Vivid Q system (GE Healthcare, Horten, Norway) with a 3.5-MHz transducer. Cine loops in parasternal long axis and apical four-, two-, and three-chamber views were recorded. Images were analyzed in cine loops triggered by the QRS complex and saved for blinded offline analysis, which was performed using dedicated software (EchoPAC 204TM, GE Healthcare, Chicago).

### **Two-dimensional and tissue Doppler echocardiography analysis.**

Standard acquisitions were recorded before the first session in accordance with the guidelines from American Society of Echocardiography (22). LV internal diameters and wall thicknesses were measured from the parasternal long axis view. LV mass was calculated by the Devereux formula and indexed to body surface area. LV volumes and LV EF were measured using the Simpson biplane method. End-diastolic volumes were obtained as preload index. LV diastolic function was assessed using early (E) and atrial (A) transmitral flow velocities, recorded in apical four-chamber view. Myocardial systolic (s0), early diastolic (e0), and atrial (a0) velocities were measured with a color-coded Doppler Tissue Imaging at the mitral annular level in apical four-chamber view. Peak e0 (i.e., average recorded on the LV septal and lateral wall) and the E/ e0 ratio was used as indexes of LV relaxation and filling pressure, respectively (23). Three separate LA volumes (i.e., maximal, LAVmax; precontraction, LAVpreA; minimal, LAVmin) were calculated using the Simpson biplane method. LAVmax was indexed to body surface area [left atrial volume index (LAVI)]. LA total emptying volume (LAVmax - LAVmin), LA total emptying fraction [(LAVmax - LAVmin)/LAVmax] 100, LA passive emptying volume (LAVmax - LAVpreA), LA passive emptying fraction

$[(LAV_{max} - LAV_{preA})/LAV_{max}] \times 100$ , LA active emptying volume ( $LAV_{preA} - LAV_{min}$ ), and LA active emptying fraction  $[(LAV_{preA} - LAV_{min})/LAV_{preA}] \times 100$  were calculated.

## **2-D strain analysis.**

Analysis of LV linear strains was conducted as previously described in our laboratory (19, 24). Global longitudinal strain (GLS) was calculated in an 18-segment model from the apical four-, two-, and three-chamber views. LA longitudinal strains were assessed and averaged from apical four- and two-chamber views. LA reservoir, conduit, and contraction functions were estimated with ventricular end diastole as the time reference to define the zero baseline for LA strain curves according to recommendations (25).

## **Hemodynamics.**

We measured aortic blood flow velocity in the ascending aorta with a 2.0-MHz continuous-wave Doppler transducer (Pedof P2D CW; GE Vingmed Ultrasound) placed at the suprasternal notch to assess stroke volume and cardiac output as previously described (26). Brachial BP was measured using an automated BP cuff integrated into the dialysis unit on the non-access arm.

## **Outcomes**

The primary outcome of the present study was the changes from T<sub>0</sub> to T<sub>peak</sub> in the LA reservoir strain. Secondary outcomes included changes in all other speckle-tracking echocardiographic-derived parameters and standard echocardiographic and central hemodynamic variables.

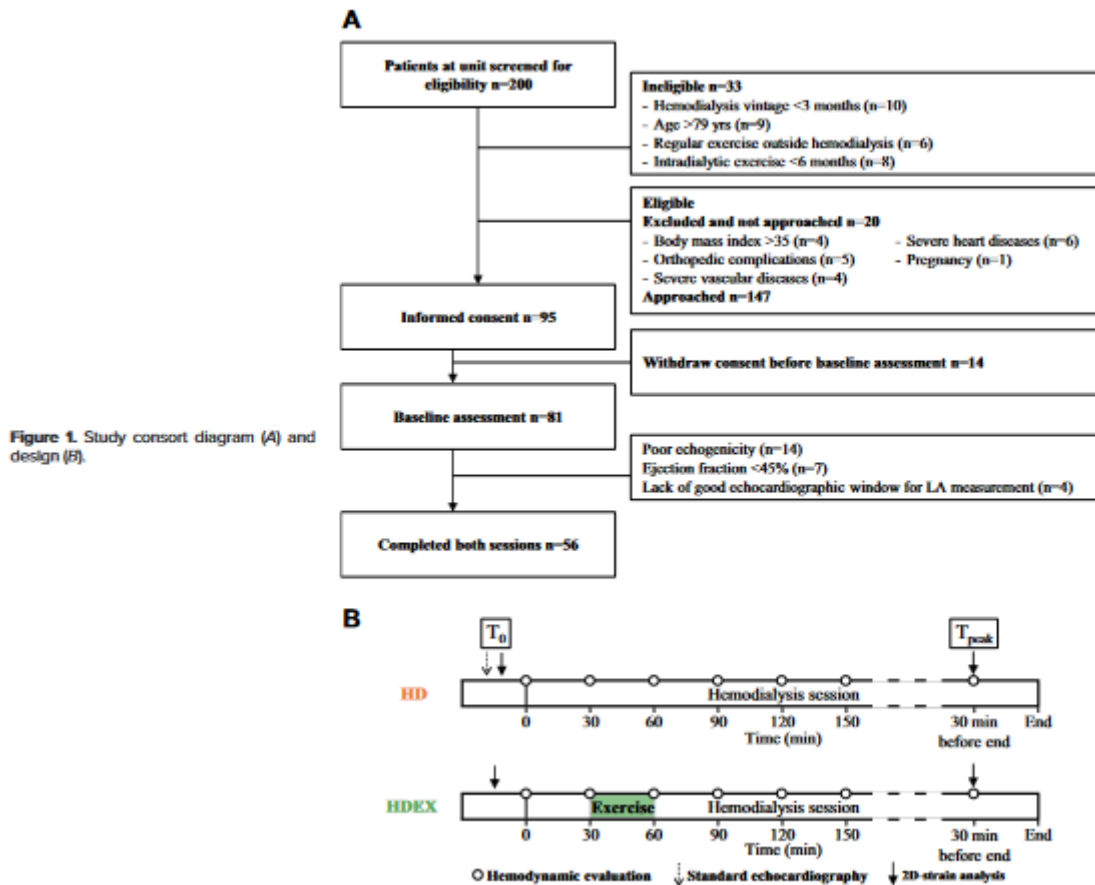


Figure 1. Study consort diagram (A) and design (B).

## Statistical Analysis

Statistical analysis was performed using IBM SPSS statistics V. 26.0 (IBM, Armonk, NY). Values are expressed as means  $\pm$  SD. Statistical significance was defined as P value  $<0.05$ . The present experiment is part of a seminal study looking at the effect of IDE on GLS changes during hemodialysis, data about minimum sample size are presented elsewhere (19). All analyses regarding the effect of IDE were based on the intention-to-treat principle. The primary and secondary outcomes were analyzed using a linear mixed-effects model, with condition (i.e., HD vs. HDEX) and time (T0 and Tpeak) as fixed effects and a random effect for patients. For subgroup analysis, the same analysis method was used adding the group as fixed effect. Post hoc analyses were also conducted with LA reservoir strain at T0 or its delta change from T0 to Tpeak in standard HD as covariate. Pearson correlations were used to investigate the association between changes from T0 to Tpeak in LA myocardial function with LA and LV echocardiographic parameters and biological and clinical data



**Table 1. Clinical characteristics**

Demographic characteristics	
Age, yr	63 ± 13
Gender, n (male/female)	40/16
Dry weight, kg	73.1 ± 15.8
Body mass index, kg/m <sup>2</sup>	25.6 ± 4.4
Dialysis vintage, years	5.5 ± 5.7
Biological data	
Hemoglobin, g/100 mL	11.9 ± 2.2
Calcium, mmol/L	2.3 ± 0.1
Potassium, mmol/L	4.9 ± 0.8
Sodium, mmol/L	138 ± 2
Creatinine, μmol/L	747 ± 262
C-reactive protein ultrasensitive, mg/L	36.5 ± 45.6
Urea, mmol/L	21.4 ± 4.9
Comorbidities, n (%)	
Diabetes	10 (18)
Hypertension	31 (55)
Coronary artery disease	6 (11)
Heart failure	9 (16)
Hyperparathyroidism	8 (14)
Peripheral vascular disease	13 (23)
Chronic kidney disease etiology, n (%)	
Glomerular nephritis	10 (18)
Immunoglobulin A nephropathy	4 (7)
Hypertensive nephropathy	11 (20)
Diabetic nephropathy	6 (11)
Congenital	2 (4)
Indeterminate	6 (11)
Other	33 (29)
Medication, n (%)	
Antiplatelet	1 (2)
Anticoagulants	11 (20)
Nitrates	1 (2)
Statins	10 (18)
Diuretics	13 (23)
Anti-arrhythmic	3 (5)
Calcium channel blockers	7 (13)
β-Blockers	18 (32)
Erythropoietin	3 (5)
Corticosteroids	3 (5)
Thyroxine	1 (2)

**Table 2. Hemodialysis parameters**

	HD	HDEX	P Value
Weight, kg			
Predialysis	75.7 ± 14.7	75.7 ± 14.8	0.97
Postdialysis	73.1 ± 14.5*	73.0 ± 14.4*	0.65
Ultrafiltration volume, L	2.66 ± 0.91	2.63 ± 0.90	0.71
Duration, min	232 ± 18	232 ± 15	0.95
Filtration rate, mL/min	354 ± 47	359 ± 24	0.47
Kt/V	1.50 ± 0.27	1.52 ± 0.32	0.63

HD, hemodialysis; HDEX, hemodialysis incorporating 30 min of constant aerobic exercise. \*P < 0.001 pre- vs. postdialysis.

## RESULTS

Baseline Characteristics and HD Parameters As previously reported (19), the trial recruited from December 2020 to February 2022. A total of 200 people receiving hemodialysis were screened and 147 individuals were approached. Out of them, 95 gave initial consent and 14 subsequently dropped out. After baseline assessments, 25 patients were excluded for LV EF lower than 45% (n = 7) and poor echogenicity (n = 14) or lack of good echocardiographic window for LA measurements (n = 4). Finally, 56 individuals were enrolled and completed both HD and HDEX sessions (Fig. 1A). The clinical characteristics are presented in Table 1. The mean age of the 56 patients was 63 ± 13 yr including 16 female participants. Body weight

at pre- and post-dialysis and all dialysis parameters were strictly similar between HD and HDEX (Table 2). Baseline standard echocardiographic data are presented in Table 3. According to guidelines (23), 30 patients presented with LA enlargement (i.e., LAVI > 34 mL/m<sup>2</sup>) and 26 patients had a normal LA morphology (i.e., LAVI ≤ 34 mL/m<sup>2</sup>).

### Cardiac Function During HD and HDEX

LV and LA conventional measurements and 2-D strain parameters at each time point are presented in Table 4. IDE did not affect the changes from T0 to Tpeak in LV end-diastolic volume, LV EF, LAVmax, LAVmin, LAVpreA, LA passive and active emptying volumes, and LA conduit and contractile strains. In contrast, there was evidence that IDE preserved our primary outcome over the hemodialysis procedure, estimated difference of change from T0 to Tpeak between HD and HDEX being significant for LA reservoir strains [3.1%, 95% confidence interval (CI): 0.4/5.8, P = 0.02; Fig. 2]. From T0 to Tpeak, LA reservoir strains decreased during HD (P < 0.001), whereas they remained unchanged during HDEX (P = 0.14). IDE also favorably impacted the changes in GLS from T0 to Tpeak (P < 0.01).

A significant correlation was obtained between changes from T0 to Tpeak in LA reservoir strain and GLS during HD (r = -0.38, P < 0.01) and HDEX (r = -0.40, P < 0.01). Between-session differences in changes from T0 to Tpeak of GLS and LA reservoir strain were also correlated (r = -0.32, P = 0.03). No significant correlation was found between difference of changes between HD and HDEX in LA reservoir strain over the procedure and ultrafiltrated volumes (r = 0.21, P = 0.15).

**Table 3. Baseline cardiac characteristics**

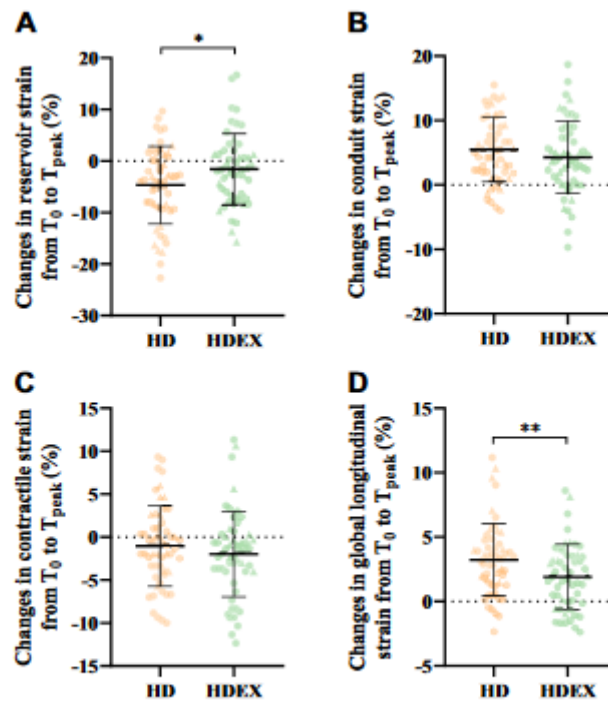
<b>2-D parameters</b>	
LV end-diastolic volume, mL	108 ± 28
LV end-systolic volume, mL	48 ± 16
Relative wall thickness	0.33 ± 0.07
LV mass index, g/m <sup>2</sup>	115 ± 33
LV ejection fraction, %	55 ± 8
<b>LV pulsed-wave Doppler</b>	
E, m/s	0.82 ± 0.19
A, m/s	0.79 ± 0.23
E/A	1.10 ± 0.29
<b>LV tissue Doppler imaging parameters</b>	
s', cm/s	6.3 ± 2.4
e', cm/s	9.9 ± 2.4
a', cm/s	8.6 ± 1.6
E/e' ratio	11.2 ± 4.7

2-D, two-dimensional; LV, left ventricle.

**Table 4.** Left ventricular and left atrial measurements at each time point

							Linear Mixed-Effects Model			
	HD			HDEX			Condition × Sequence	Condition × Time		
	T <sub>0</sub>	T <sub>peak</sub>	P Value <sup>a</sup>	T <sub>0</sub>	T <sub>peak</sub>	P Value <sup>a</sup>		P Value	Estimated Difference <sup>b</sup>	(95% CI)
<b>Conventional measurements</b>										
LV end-diastolic volume, mL	111 ± 27	92 ± 25	<0.001	110 ± 28	92 ± 23	<0.001	0.44	1.5	(-6.8/9.8)	0.72
LV ejection fraction, %	54 ± 8	50 ± 8	<0.001	54 ± 6	50 ± 8	<0.001	0.40	1.1	(-1.9/4.3)	0.47
LA maximal volume, mL	74 ± 12	55 ± 20	<0.001	73 ± 19	57 ± 18	<0.001	0.75	3.7	(-1.6/9.1)	0.17
LA minimal volume, mL	31 ± 15	25 ± 13	<0.001	31 ± 13	24 ± 10	<0.001	0.89	-1.3	(-4.7/2.1)	0.45
LA pre-A wave volume, mL	52 ± 19	44 ± 18	<0.001	52 ± 17	44 ± 17	<0.001	0.98	0.3	(-4.7/5.3)	0.90
LA total emptying volume, mL	43 ± 11	29 ± 10	<0.001	41 ± 13	33 ± 12	<0.001	0.70	5.0	(1.18.8)	0.01
LA total emptying fraction, %	59 ± 10	55 ± 10	<0.001	58 ± 11	58 ± 12	<0.001	0.85	4.7	(0.6/8.8)	0.03
LA passive emptying volume, mL	22 ± 9	11 ± 6	<0.001	20 ± 11	12 ± 9	<0.001	0.41	3.4	(-0.2/7.0)	0.07
LA passive emptying fraction, %	31 ± 11	20 ± 10	<0.001	28 ± 13	22 ± 15	0.002	0.32	4.1	(1.0/9.2)	0.11
LA active emptying volume, mL	21 ± 8	19 ± 7	0.04	21 ± 8	21 ± 10	0.74	0.78	1.7	(-1.5/4.5)	0.29
LA active emptying fraction, %	29 ± 8	35 ± 8	<0.001	30 ± 10	36 ± 14	<0.001	0.30	0.3	(-4.3/4.9)	0.89
<b>2-D strain parameters</b>										
LV global longitudinal strain, %	-18.1 ± 3.4	-15.0 ± 4.0	<0.001	-18.1 ± 3.3	-16.4 ± 3.4	<0.001	0.97	-1.2	(-2.1/-0.3)	0.009
LA reservoir phase, %	31.5 ± 8.9	26.9 ± 7.7	<0.001	30.7 ± 9.8	29.2 ± 8.9	0.14	0.33	3.1	(0.4/5.8)	0.02
LA conduit phase, %	-16.4 ± 5.6	-11.0 ± 4.2	<0.001	-16.0 ± 6.7	-11.7 ± 5.0	<0.001	0.45	-1.1	(-3.0/0.8)	0.24
LA contractile phase, %	-15.1 ± 5.0	-16.1 ± 4.8	0.11	-15.3 ± 4.8	-17.3 ± 5.4	0.004	0.48	-1.0	(-2.8/0.8)	0.26

Negative estimated differences for negative data like LV global longitudinal strain, LA reservoir, or contractile phases and positive estimated differences for positive data like LA reservoir phase or LV and LA volumes indicate the superiority and cardioprotective effect of HDEX. The parameters were estimated by maximum likelihood, and P values were generated by Wald tests. CI, confidence interval; HD, hemodialysis; HDEX, hemodialysis incorporating 30 min of constant aerobic exercise; LA, left atrial; LV, left ventricle. <sup>a</sup>P value for change within the same condition, analyzed using one-sample t test; <sup>b</sup>estimated difference of change from T<sub>0</sub> to T<sub>peak</sub> between HD and HDEX generated by the linear mixed-effects regression model, with HD and T<sub>0</sub> as reference factors.



**Figure 2.** Effect of intradialytic exercise on left atrial reservoir (A), conduit (B), contractile strains (C), and left ventricular global longitudinal strain (D) in men (●) and women (▲). LA, left atrial; LV, left ventricular. Estimated differences: \*P < 0.05; \*\*P < 0.01.

## Effects of LA Remodeling on LA Function During HD and HDEX

A significant between-session difference of changes from T0 to Tpeak in LA reservoir strain was observed between patients with normal (i.e., LAVI  $\leq 34$  mL/m<sup>2</sup>) and dilated (i.e., LAVI  $> 34$  mL/m<sup>2</sup>) LA (point estimates: 6.5%, 95% CI: 11.8/1.2, P = 0.02) (Fig. 3A). There was overwhelming evidence that IDE favorably impacted LA reservoir strain changes over the hemodialysis procedure in patients with normal LA morphology (HD:  $6.9 \pm 8.0\%$ , HDEX:  $0.3 \pm 7.6\%$ , point estimates: 6.6, 95% CI: 2.2/11.0, P < 0.01), whereas the changes during HD and HDEX were similar in patients with enlarged LA (HD:  $2.8 \pm 6.7\%$ , HDEX:  $2.7 \pm 6.1\%$ , point estimates: 0.4%, 95% CI: 3.1/3.2, P = 0.9) (Fig. 3B). Such results were confirmed with either the absolute changes from T0 to Tpeak in LA reservoir strain or with LA reservoir strain at T0 during HD used as covariates. LAVI correlated significantly with both the changes from T0 to Tpeak in LA reservoir strain during HD ( $r = 0.42$ , P < 0.01) and the difference of changes from T0 to Tpeak between conditions of LA reservoir strain ( $r = -0.40$ , P < 0.01) (Fig. 4). Hemodynamic Changes During HD and HDEX IDE did not modify the trajectory from T0 to Tpeak of all hemodynamic parameters (Table 5). There were no differences between HD and HDEX at each time point, except during the 30-min exercise, where higher HR and cardiac output values as well as SBP and MBP were obtained (P > 0.05 in each case, data not shown).

## DISCUSSION

To the best of our knowledge, this is the first study reporting the effects of IDE on the different phases of LA function. Our major findings highlight first that a short duration IDE at moderate intensity is effective in preventing hemodialysis-associated decline in LA reservoir function and second that such a cardioprotection is abolished in patients with enlarged LA.

### Effects of Hemodialysis on LA Mechanics

The LA function plays an important role in cardiac performance by modulating LV function. Several studies have reported hemodialysis-related impairment in LV function, but very few have evaluated the impacts of this excess fluid removal procedure on LA function. In the present study, volumetric indexes of LA function decreased from T0 to Tpeak during HD, agreeing with previous studies (17). These measurements are, however, largely influenced by loading conditions (27), which, in the context of volume depletion such as found in

hemodialysis, are of particular importance. LA strain is less load-dependent than LA conventional parameters (16) and therefore reflects more accurately changes in intrinsic contractility/relaxation properties. In our study, LA reservoir and conduit strains decreased during HD, whereas contractile ones were globally preserved (Fig. 2 and Table 4). Today, there is limited data describing the changes in LA mechanics during hemodialysis in patients with ESKD. The few available studies (17, 28) also reported decrements in LA strain during hemodialysis, with changes correlating with blood volume depletion. Even if no significant correlation was obtained between absolute changes from T0 to Tpeak in LA reservoir strain with ultrafiltrated volume, the influence of preload alterations on our results cannot totally be excluded. LA reservoir function and LV systolic function are modulated by both LA relaxation and compliance properties (15). In our study, the absolute changes in LA reservoir strain during HD correlated with the absolute changes in GLS, emphasizing the close interdependence between the function of these two cavities. The transient hemodialysis-associated LV systolic dysfunction, resulting from disturbances in myocardial segmental perfusion, is well described in the literature (12–14). Such a phenomenon could very likely be involved also in the explanation of the hemodialysis-associated alteration in LA reservoir strain. Of note, in an experimental model, Barbier et al. (29) reported that acute LV regional ischemia impairs not only LV systolic function but also LA function, evaluated using volumetric measurements during the reservoir phase, and LA compliance and relaxation properties. The repetitive nature of myocardial ischemic insults and transient dysfunction due to hemodialysis may, in the long term, yield permanent regional myocardial dysfunction, conferring an increased risk of cardiac events and mortality (18), necessitating, therefore, the application of countermeasures during hemodialysis.

### **Benefits of IDE on LA Mechanics**

The salient feature from the present study is the beneficial effect of acute IDE in preventing the hemodialysis-related decline in LA reservoir function. First, IDE did not alter hemodynamic parameters (BP and cardiac output), confirming the safety of this type of intervention. Moreover, loading conditions and ultrafiltration volumes were strictly similar between HD and HDEX, suggesting that the benefits of IDE on LA reservoir function were not related to hemodynamic factors. In our study, a similar result favoring IDE intervention was also demonstrated on GLS changes from T0 to Tpeak. Furthermore, between-session differences of changes in GLS and LA reservoir strain were correlated, indicating that the relative preservation of LV systolic function by IDE partially explains that of LA reservoir function. Indeed, LV and LA are mechanically connected and share the motion of the mitral ring. Thus, longitudinal shortening of the LV implies expansion of the LA, promoting LA reservoir strain. Other mechanisms must be advanced. The cardioprotection conferred by IDE on LV systolic function has already been explained via a reduction of hemodialysis-induced perfusion abnormalities (20). Since ischemia also impairs LA relaxation and compliance (29), we can reasonably speculate that IDE might have also preserved LA myocardial perfusion

(and thus its relaxation properties and compliance), thereby limiting the impairment in LA reservoir function. Further studies are needed to explore the mechanisms behind IDE-induced cardioprotection.

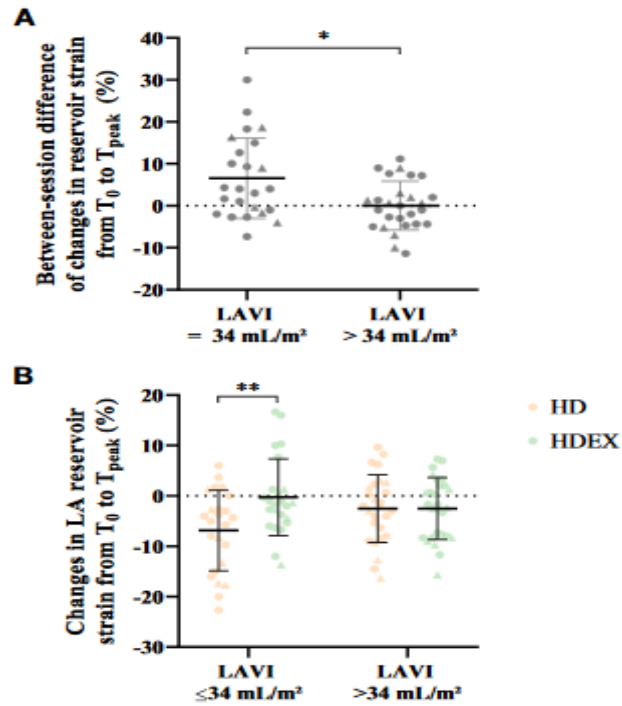
### Effect of LA Remodeling on LA Mechanics

During HDEX In a subgroup analysis, we were able to demonstrate that IDE did not affect the trajectory of LA reservoir strain in patients presenting LA enlargement. In contrast, individuals with normal LA morphology benefited from acute IDE, with a lower decrease in LA reservoir strain during HDEX compared with HD (Fig. 3). Furthermore, a correlation between LAVI and the difference between HD and HDEX of the absolute changes from  $T_0$  to  $T_{peak}$  in LA reservoir strain was obtained ( $r = -0.40$ ,  $P < 0.01$ ). In patients with cardiovascular risk factors, LA enlargement represents maladaptive structural and functional cardiac remodeling. In many diseases, LA dysfunction precedes LA geometric remodeling and even abnormal LV longitudinal function (30, 31). Thus, we can hypothesize that patients with LA hypertrophy may not benefit from IDE-induced cardioprotection due to advanced pathological structural and functional remodeling affecting the whole myocardium. Pathological LA remodeling is notably associated with increased interstitial fibrosis (32). Of note, Yan et al. (33) in an experimental model highlighted that myocardial fibrosis weakens the cardioprotective effects of ischemic preconditioning. Similar mechanisms might be advanced to partially explain the absence of benefits of acute IDE in our subgroup of patients with LA enlargement.

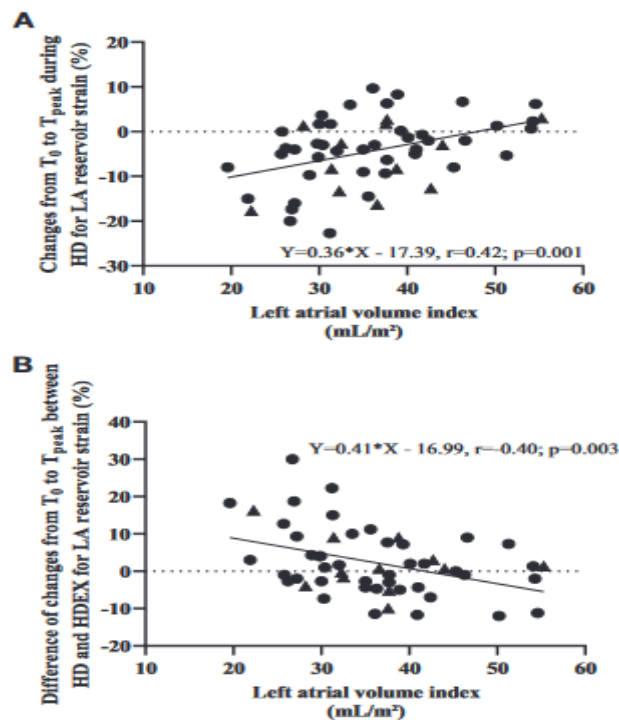
**Table 5. Hemodynamic parameters at each time point**

	HD			HDEX			Linear Mixed-Effects Model			
	$T_0$	$T_{peak}$	P Value <sup>a</sup>	$T_0$	$T_{peak}$	P Value <sup>a</sup>	Condition × Sequence P Value	Condition × Time		
								Estimated Difference <sup>b</sup>	(95% CI)	P Value
Heart rate, beats/min	70 ± 11	71 ± 12	0.41	70 ± 9	71 ± 11	0.71	0.56	-2	(-4/3)	0.71
Left ventricular stroke volume, mL	69 ± 33	57 ± 24	<0.001	70 ± 33	57 ± 25	<0.001	0.69	-0.6	(-8.1/6.9)	0.88
Cardiac output, L/min	4.9 ± 2.4	4.0 ± 1.8	<0.001	4.8 ± 2.2	4.1 ± 2.0	<0.001	0.71	0.1	(-0.5/0.7)	0.75
Systolic blood pressure, mmHg	138 ± 18	129 ± 23	0.001	136 ± 21	129 ± 21	0.003	0.04	2	(-5/9)	0.60
Diastolic blood pressure, mmHg	76 ± 16	72 ± 16	0.02	73 ± 16	72 ± 16	0.39	0.01	3	(-2/7)	0.23
Mean blood pressure, mmHg	96 ± 16	90 ± 16	0.001	93 ± 17	90 ± 16	0.03	0.11	2	(-2/7)	0.31

The parameters were estimated by maximum likelihood, and P values were generated by Wald tests. CI, confidence interval; HD, hemodialysis; HDEX, hemodialysis incorporating 30 min of constant aerobic exercise. <sup>a</sup>P value for change within the same condition, analyzed using one-sample t test; <sup>b</sup>estimated difference of change from  $T_0$  to  $T_{peak}$  between HD and HDEX generated by the linear mixed-effects regression model, with HD and  $T_0$  as reference factors.



**Figure 3.** Effect of intradialytic exercise on left atrial reservoir strain according to left atrial morphology in men (●) and women (▲). Between-session difference (A) and changes during HD and HDEX (B) in left atrial reservoir strain over the hemodialysis procedure. HD, hemodialysis; HDEX, hemodialysis incorporating 30 min of constant aerobic exercise; LA, left atrial; LAVI, left atrial volume index. Estimated differences: \* $P < 0.05$ ; \*\* $P < 0.01$ .



**Figure 4.** Relationship between baseline left atrial volume index and changes from  $T_0$  to  $T_{peak}$  in left atrial (LA) reservoir strain during HD (A) and its difference of changes between HD and HDEX over the procedure (B) in men (●) and women (▲). HD, conventional hemodialysis; HDEX, hemodialysis incorporating 30 min of constant aerobic exercise.

## **Clinical Implications**

LA reservoir function constitutes an independent predictor of cardiovascular mortality and major adverse cardiovascular events in patients with chronic kidney disease (34). In the present study, the preservation of LA reservoir function from T<sub>0</sub> to T<sub>peak</sub> during HDEX compared with HD (3.1%, 95% CI: 0.4/5.8, P = 0.02) gives preliminary evidence of the cardioprotection conferred by IDE. This is of major clinical relevance in patients undergoing hemodialysis because the hazards ratio for prediction of major adverse cardiovascular events increased by 4% per 1% decrease in LA reservoir strain (35). Moreover, atrial fibrillation is a frequent comorbid condition in patients with ESKD on hemodialysis, with a prevalence of up to 27% (36). The pathophysiology of atrial fibrillation is complex including volume overload, inflammation, or uremia (37). Interestingly, Papadopoulos et al. (38) reported that LA reservoir strain impairment is an independent predictor of atrial fibrillation, suggesting that IDE might help in limiting the occurrence and progression of atrial fibrillation. Whether the transient improvement in LA reservoir strain conferred by IDE when repeated on each dialysis translates into improved clinical outcomes remains to be determined.

## **Limitations**

There are some limitations to this study, which should be acknowledged. In the present study, we used a single mode, duration, and intensity of exercise. Further studies are needed to evaluate the optimal pattern of exercise (e.g., continuous vs. interval exercise) to induce the greatest cardioprotective benefits. Our very restrictive exclusion criteria (especially body mass index >35 kg·m<sup>2</sup> and ejection fraction <45%) helped to control confounder factors such as severe obesity but limit the universality of our results. We have hypothesized that the loss in cardioprotective effects of intradialytic exercise was due to an increase in myocardial fibrosis in patients with LA enlargement. However, we were unable to corroborate this with the extent of collagen fibers in this population, which was beyond the scope of this study. We did not evaluate the time of recovery of the HD-induced dysfunction. Finally, we did not evaluate the long-term outcomes of IDE, as this was also outside the purview of this study. Future studies are needed to determine the cardiovascular effect of chronic IDE, as well as its effect on cardiovascular events, mortality, and occurrence of LA fibrillation in individuals with ESKD.



## **Conclusions**

A single bout of 30 min of intradialytic cycling was sufficient to limit the hemodialysis-related reduction in LA reservoir function. Such a cardioprotective effect was, however, lost in patients with pathological LA remodeling. IDE represents an interesting non-pharmaceutical therapeutic strategy to attenuate acute hemodialysis-related cardiac complications. Further studies are needed to evaluate the clinical impacts of the repetitive cardioprotective effects of IDE on LA function.

### **DATA AVAILABILITY**

Source data for this study are openly available at <https://doi.org/10.6084/m9.figshare.24648246.v1>.

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### **DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

C.M. and P.O. conceived and designed research; C.M., M.J., A.G., S.N., and P.O. performed experiments; C.M., M.J., S.N., and P.O. analyzed data; C.M., M.J., and P.O. interpreted results of experiments; C.M., M.J., and P.O. prepared figures; C.M., M.J., and P.O. drafted manuscript; C.M., M.J., and P.O. edited and revised manuscript; C.M., M.J., L.P., A.G., M.I., C.T.-B., S.N., S.M., J.-P.C., and P.O. approved final version of manuscript.

## REFERENCES

1. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl* (2011) 12: 7–11, 2022. doi:10.1016/j.kisu. 2021.11.003.
2. Bello AK, Okpechi IG, Osman MA, Cho Y, Htay H, Jha V, Wainstein M, Johnson DW. Epidemiology of haemodialysis outcomes. *Nat Rev Nephrol* 18: 378–395, 2022. doi:10.1038/s41581-022-00542-7.
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardio-vascular disease in chronic renal disease. *Am J Kidney Dis* 32: S112– S119, 1998. doi:10.1053/ajkd.1998.v32.pm9820470.
4. Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, et al. US Renal Data System 2015 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 67, Suppl 1: S1– S305, 2016. doi:10.1053/j.ajkd.2015.12.014.
5. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant* 11: 1277–1285, 1996.
6. Cibulka R, Racek J. Metabolic disorders in patients with chronic kidney failure. *Physiol Res* 56: 697–705, 2007. doi:10.33549/physiolres. 931128.
7. Plawecki M, Morena M, Kuster N, Chenine L, Leray-Moragues H, Jover B, Fesler P, Lotierzo M, Dupuy AM, Klouche K, Cristol JP. sST2 as a new biomarker of chronic kidney disease-induced cardiac remodeling: impact on risk prediction. *Mediators Inflamm* 2018:3952526, 2018. doi:10.1155/2018/3952526.
8. Fraser SD, Roderick PJ, May CR, McIntyre N, McIntyre C, Fluck RJ, Shardlow A, Taal MW. The burden of comorbidity in people with chronic kidney disease stage 3: a cohort study. *BMC Nephrol* 16: 193, 2015 [Erratum in *BMC Nephrol* 21: 543, 2020]. doi:10.1186/s12882-015-0189-z.

9. Kim SJ, Han SH, Park JT, Kim JK, Oh HJ, Yoo DE, Yoo TH, Kang SW, Choi KH. Left atrial volume is an independent predictor of mortality in CAPD patients. *Nephrol Dial Transplant* 26: 3732–3739, 2011. doi:10.1093/ndt/gfr118.
10. Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. *Lancet* 388: 276–284, 2016. doi:10.1016/S0140-6736(16)30508-6.
11. McIntyre CW. Effects of hemodialysis on cardiac function. *Kidney Int* 76: 371–375, 2009. doi:10.1038/ki.2009.207.
12. McGuire S, Horton EJ, Renshaw D, Jimenez A, Krishnan N, McGregor G. Hemodynamic instability during dialysis: the potential role of intradialytic exercise. *Bio Med Res Int* 2018: 8276912, 2018. doi:10.1155/2018/8276912.
13. Dasselaar JJ, Slart RH, Knip M, Pruijm J, Tio RA, McIntyre CW, de Jong PE, Franssen CF. Haemodialysis is associated with a pronounced fall in myocardial perfusion. *Nephrol Dial Transplant* 24: 604–610, 2009. doi:10.1093/ndt/gfn501.
14. McIntyre CW, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker CS, Camici PG. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol* 3: 19–26, 2008. doi:10.2215/CJN.03170707.
15. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left atrial structure and function, and left ventricular diastolic dysfunction: JACC state-of-the-art review. *J Am Coll Cardiol* 73: 1961–1977, 2019. doi:10.1016/j.jacc.2019.01.059.
16. Leischik R, Littwitz H, Dworrak B, Garg P, Zhu M, Sahn DJ, Horlitz M. Echocardiographic evaluation of left atrial mechanics: function, history, novel techniques, advantages, and pitfalls. *Biomed Res Int* 2015: 765921, 2015. doi:10.1155/2015/765921.
17. Ünücu S, Yamak BA, Sezenoz B, Şahinarslan A, Arınsoy ST. Left atrial contractile longitudinal strain determines intrinsic left atrial function regardless of load status and left ventricular deformation. *Int J Cardiovasc Imaging* 37: 3245–3253, 2021. doi:10.1007/s10554-021-02324-x.
18. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 4: 914–920, 2009. doi:10.2215/CJN.03900808.
19. Josse M, Patrier L, Isnard M, Turc-Baron C, Grandperrin A, Nottin S, Mandigout S, Cristol JP, Maufrais C, Obert P. Cardioprotective effect of acute intradialytic exercise: a comprehensive speckle-tracking echocardiography analysis. *J Am Soc Nephrol* 34: 1445–1455, 2023. doi:10.1681/ASN.000000000000149.
20. McGuire S, Horton EJ, Renshaw D, Chan K, Jimenez A, Maddock H, Krishnan N, McGregor G. Cardiac stunning during haemodialysis: the therapeutic effect of intra-dialytic exercise. *Clin Kidney J* 14: 1335–1344, 2019. doi:10.1093/ckj/sfz159.

21. Penny JD, Salerno FR, Brar R, Garcia E, Rossum K, McIntyre CW, Bohm CJ. Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning. *Nephrol Dial Transplant* 34: 1917–1923, 2019. doi:10.1093/ndt/gfy376.
22. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 16: 233–270, 2015 [Erratum in *Eur Heart J Cardiovasc Imaging* 17: 412,2016] doi:10.1093/ehjci/jev014.
23. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 29: 277–314, 2016. doi:10.1016/j.echo.2016.01.011.
24. Maufrais C, Schuster I, Doucende G, Vitiello D, Rupp T, Dautat M, Obert P, Nottin S. Endurance training minimizes age-related changes of left ventricular twist-untwist mechanics. *J Am Soc Echocardiogr* 27: 1208–1215, 2014. doi:10.1016/j.echo.2014.07.007.
25. Badano LP, Koliass TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, D’Hooge J, Donal E, Fraser AG, Marwick T, Mertens L, Popescu BA, Sengupta PP, Lancellotti P, Thomas JD, Voigt JU; Industry representatives; Reviewers: This document was reviewed by members of the 2016–2018 EACVI Scientific Documents Committee. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/ Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 19: 591–600, 2018 [Erratum in *Eur Heart J Cardiovasc Imaging* 19: 830–833, 2018]. doi:10.1093/ehjci/jey042.
26. Vinet A, Nottin S, Lecoq AM, Guenon P, Obert P. Reproducibility of cardiac output measurements by Doppler echocardiography in pre- pubertal children and adults. *Int J Sports Med* 22: 437–441, 2001. doi:10.1055/s-2001-16241.
27. Genovese D, Singh A, Volpato V, Kruse E, Weinert L, Yamat M, Mor-Avi V, Addetia K, Lang RM. Load dependency of left atrial strain in normal subjects. *J Am Soc Echocardiogr* 31: 1221–1228, 2018. doi:10.1016/j.echo.2018.07.016.
28. Park CS, Kim YK, Song HC, Choi EJ, Ihm SH, Kim HY, Youn HJ, Seung KB. Effect of preload on left atrial function: evaluated by tissue Doppler and strain imaging. *Eur Heart J Cardiovasc Imaging* 13: 938–947, 2012. doi:10.1093/ehjci/jes069.
29. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. *Circulation* 100: 427–436, 1999. doi:10.1161/01.cir.100.4.427.

30. Zhou D, Yang W, Yang Y, Yin G, Li S, Zhuang B, Xu J, He J, Wu W, Jiang Y, Sun X, Wang Y, Sirajuddin A, Zhao S, Lu M. Left atrial dysfunction may precede left atrial enlargement and abnormal left ventricular longitudinal function: a cardiac MR feature tracking study. *BMC Cardiovasc Disord* 22: 99, 2022. doi:10.1186/s12872-022-02532-w.
31. Bouwmeester S, van der Stam JA, van Loon SLM, van Riel NAW, Boer AK, Dekker LR, Scharnhorst V, Houthuizen P. Left atrial reservoir strain as a predictor of cardiac outcome in patients with heart failure: the HaFaC cohort study. *BMC Cardiovasc Disord* 22: 104, 2022. doi:10.1186/s12872-022-02545-5.
32. Thomas L, Abhayaratna WP. Left atrial reverse remodeling: mechanisms, evaluation, and clinical significance. *JACC Cardiovasc Imaging* 10: 65–77, 2017. doi:10.1016/j.jcmg.2016.11.003.
33. Yan T, Zhu QM, Li HX, Wang TH, Zhang GH, Sun L. Effects of myocardial fibrosis on ischemic preconditioning against myocardial ischemia-reperfusion injury in type 2 diabetic rats. *Zhonghua Yi Xue Za Zhi* 101: 3857–3863, 2021. doi:10.3760/cma.j.cn112137-20211025-02356.
34. Gan GCH, Kadappu KK, Bhat A, Fernandez F, Gu KH, Cai L, Byth K, Eshoo S, Thomas L. Left atrial strain is the best predictor of adverse cardiovascular outcomes in patients with chronic kidney disease. *J Am Soc Echocardiogr* 34: 166–175, 2021. doi:10.1016/j.echo.2020.09.015.
35. Sun M, Xing Y, Guo Y, Cao X, Nie Y, Shu X. Left atrial reservoir strain is an outstanding predictor of adverse cardiovascular outcomes in patients undergoing maintenance hemodialysis: assessment via three-dimensional speckle tracking echocardiography. *Clin Cardiol* 45: 549–557, 2022. doi:10.1002/clc.23815.
36. Konigsbrugge O, Ay C. Atrial fibrillation in patients with end-stage renal disease on hemodialysis: magnitude of the problem and new approach to oral anticoagulation. *Res Pract Thromb Haemost* 3: 578–588, 2019. doi:10.1002/rth2.12250.
37. Korantzopoulos PG, Goudevenos JA. Atrial fibrillation in end-stage renal disease: an emerging problem. *Kidney Int* 76: 247–249, 2009. doi:10.1038/ki.2009.144.
38. Papadopoulos CE, Pagourelis E, Bakogiannis C, Triantafyllou K, Baltoumas K, Kassimatis E, Zioutas D, Siskos D, Tzikas S, Fragakis N, Papagianni A, Vassilikos V. Left atrial deformation as a potent predictor for paroxysmal atrial fibrillation in patients with end stage renal disease. *Int J Cardiovasc Imaging* 34: 1393–1401, 2018. doi:10.1007/s10554-018-1353-x.

