

- modelling approach based on the data of the French Language Peritoneal Dialysis Registry. *Nephrol Dial Transplant* 2017; 32: 1018–1023
46. Duquenois S, Bechade C, Verger C *et al*. Is peritonitis risk increased in elderly patients on peritoneal dialysis? Report from the French Language Peritoneal Dialysis Registry (RDPLF). *Perit Dial Int* 2016; 36: 291–296
47. Lee MB, Bargman JM. Survival by dialysis modality—who cares? *Clin J Am Soc Nephrol* 2016; 11: 1083–1087
48. Chanouzas D, Ng KP, Fallouh B *et al*. What influences patient choice of treatment modality at the pre-dialysis stage? *Nephrol Dial Transplant* 2012; 27: 1542–1547
49. Dahlerus C, Quinn M, Messersmith E *et al*. Patient perspectives on the choice of dialysis modality: Results from the Empowering Patients on Choices for Renal Replacement Therapy (EPOCH-RRT) study. *Am J Kidney Dis* 2016; 68: 901–910

Received: 31.8.2017; Editorial decision: 22.12.2017

Nephrol Dial Transplant (2018) 33: 1419–1427

doi: 10.1093/ndt/gfy041

Advance Access publication 26 March 2018

Systemic haemodynamics in haemodialysis: intradialytic changes and prognostic significance

Stefanie Haag¹, Björn Friedrich², Andreas Peter^{1,3,4}, Hans-Ulrich Häring^{1,3,4}, Nils Heyne^{1,3,4} and Ferruh Artunc^{1,3,4}

¹Department of Internal Medicine, Division of Endocrinology, Diabetology, Vascular Disease, Nephrology and Clinical Chemistry, University Hospital Tübingen, Tübingen, Germany, ²Nephrological Center, Leonberg, Germany, ³Institute of Diabetes Research and Metabolic Diseases (IDM) of the Helmholtz Center Munich, University of Tübingen, Tübingen, Germany and ⁴German Center for Diabetes Research (DZD), Tübingen, Germany

Correspondence and offprint requests to: Ferruh Artunc; E-mail: ferruh.artunc@med.uni-tuebingen.de

ABSTRACT

Background. Although haemodialysis (HD) leads to alterations of systemic haemodynamics that can be monitored using dilution methods, there is a lack of data on the diagnostic and prognostic significance of haemodynamic monitoring during routine HD.

Methods. In this multicentre study, we measured cardiac index (CI), access flow (AF) and central blood volume index (CBVI) during a single HD session in stable HD patients ($n = 215$) using the Transonic HD03 monitor (Transonic, Ithaca, NY, USA). Systemic CI (SCI) was defined as CI corrected for AF. In a subset of patients ($n = 82$), total end-diastolic volume index (TEDVI) and total ejection fraction (TEF) were derived from dilution curves. Data were correlated with clinical parameters, cardiac biomarkers and bioimpedance measurements (body composition monitor; Fresenius Medical Care, Homburg, Germany). Mortality was assessed prospectively after a median follow-up of 2.6 years.

Results. Median CI, CBVI and AF were 2.8 L/min/m² (interquartile range 2.4–3.4), 15 mL/kg (14.5–15.7) and 980 mL/min (740–1415), respectively, at the beginning of HD. At the end of HD, CI, CBVI and AF significantly fell by –10% (–22 to 3, $P < 0.0001$), –9% (–23 to 3, $P < 0.0001$) and –4% (–13 to 5, $P = 0.0004$), respectively. Peripheral resistance (PR) increased

slightly ($P = 0.01$) and blood pressure fell by –6/–3 mmHg to 128/63 mmHg ($P < 0.0001$). Independent predictors of Δ CI were age and ultrafiltration rate, whereas AF, overhydration and PR were protective. TEF was strongly associated with mortality [area under the dilution curve 0.77, $P < 0.0001$], followed by TEDVI (0.72, $P = 0.0002$) and SCI (0.60, $P = 0.02$).

Conclusions. HD leads to a reduction of CI due to ultrafiltration. Haemodynamic monitoring identifies a significant number of HD patients with cardiac impairment that are at risk for increased mortality.

Keywords: cardiac index, haemodialysis, haemodynamics, prognosis, ultrasound dilution

INTRODUCTION

Haemodialysis (HD) patients suffer from high cardiovascular morbidity and mortality that is age-dependently increased 8- to 100-fold when compared with the general population [1–3]. Congestive heart failure with reduced systolic function is one of the most prominent determinants of cardiovascular mortality [4, 5]. It is associated with pump failure and sudden cardiac death [6, 7] and reflected by elevated levels of the cardiac biomarkers troponin and natriuretic peptides [8–10]. Cardiac

function in HD patients is mainly evaluated using echocardiography, which is non-invasive and can be performed during a HD session. However, echocardiographic assessment of cardiac function is operator dependent, and haemodynamic data such as ejection fraction or stroke volume (SV) must be estimated from time-consuming image acquisition and calculations.

Cardiac output (CO) is the most fundamental haemodynamic parameter. It is measured by various invasive and non-invasive methods based on imaging (echocardiography/magnetic resonance [MR]), oxygen consumption (Fick principle) or indicator dilution techniques. The latter is most widely used in clinical practice and relies on the Stewart-Hamilton equation [volume of injected indicator divided by the area under the dilution curve (AUC)]. In 1995, ultrasound dilution based on the decrease of ultrasound velocity in the blood after injection of saline was introduced by Krivitski [11, 12] to measure vascular access flow (AF) in HD patients. Subsequently, Krivitski and Depner [13] expanded the ultrasound dilution technique to measure CO with high accuracy in HD patients. The method has been validated in a porcine study against a transit-time ultrasound flow probe that measures blood flow directly in the ascending aorta [14] and against thermodilution in patients undergoing cardiac surgery [15]. CO monitoring during HD is thought to detect deterioration of systemic haemodynamics before clinical events such as hypotension or syncope occurs [13, 16]. Even in the absence of an event, CO monitoring could identify those HD patients with critically low CO—be it at the beginning or at the end of HD—that might be a risk factor for sudden death and increased mortality. However, there are no large studies on CO monitoring and its prognostic significance, and it is unclear if CO monitoring is useful during routine HD, or only in individual patients with known cardiac impairment.

In this study, we attempted to better define the role of haemodynamic monitoring of HD patients. To this end, we measured CO and other newly introduced haemodynamic parameters [17] at the beginning and at the end of a single HD session in the largest cohort of stable HD patients up to this time. We analysed intradialytic changes of haemodynamics, its predictors and the prognostic significance of the haemodynamic parameters over 2.6 years.

MATERIALS AND METHODS

Patients and cohort

This prospective multicentre study included stable prevalent HD patients from four outpatient dialysis centres in Southwest Germany (Tübingen, Leonberg, Herrenberg and Sindelfingen) during July 2014 to August 2015. Patients with an arteriovenous (AV) access (fistula or graft) were included after they provided written informed consent. Patients with dialysis catheters had to be excluded because haemodynamic measurements are not feasible in a venovenous circuit. Patients with a stenosed access who were characterized by recirculation >0% after cannulation had to be excluded because this causes inaccurate CO values as some of injected saline will recirculate in the AV access instead of going to the cardiovascular system. These patients were subsequently referred to a vascular surgeon at the discretion of the

treating nephrologist. The study was in accordance with the Declaration of Helsinki and approved by the local ethics committee of the University of Tübingen (614/2014BO2).

Haemodynamic monitoring

Haemodynamics were determined at the beginning and at the end of a single routine HD session (for details see Table 1) using the Transonic HD03 monitor (Transonic, Ithaca, NY, USA). This device measures AF (mL/min), CO (L/min) and central blood volume (CBV, mL) from the decrease of the ultrasound velocity in the blood after rapid injection of a 30-mL saline bolus. A representative dilution curve is shown in Supplementary data, Figure S1. CBV represents the blood volume in the thoracic cavity in the large vessels, lung and heart and is calculated from the transit time of the bolus and CO [17]. The equation is given in the legend of Supplementary data, Figure S1. The coefficient of variation of CO and CBV measurement was reported as $4.3 \pm 3.8\%$ and $4.1 \pm 3.8\%$ from 3488 values duplicated within 5 min [13]. Special attention was given that the two needles had been inserted one after the another in the same branch of an AV fistula. After exclusion of patients with any recirculation >0% and measurement of AF (mL/min) according to manufacturer's instructions, CO and CBV were determined by rapid injection of a warm 30-mL saline bolus into the venous line using a special adaptor (Flow-QC tubing, Transonic). CO was measured once per patient at the beginning (within 20 min) and once at the end of HD (within the last 20 min). Adequacy of the result was ascertained from the dilution curve. In the case of an erroneous measurement indicated by the message 'Repeat' on the screen HD03 monitor, another bolus was applied. CO was indexed to body surface area yielding cardiac index (CI, L/min/m²) and CBV index was normalized to body weight (CBVI, mL/kg). Peripheral resistance (PR, mmHg/L/min/m²) was calculated by dividing mean arterial pressure by CI. Correction of CO for AF (CO-AF) and indexing yielded systemic CI (SCI, L/min/m²) which reflects CI that is available for whole-body perfusion. In a subset of patients ($n = 82$), total end-diastolic volume index (TEDVI, mL/kg) was derived from the available dilution curves that represent the sum of the end-diastolic volumes of four chambers (i.e. right and left atria and ventricles) [13, 17]. Its calculation is based on the assumption that the higher spread of the dilution curve at the arterial line compared with that at the venous line is due to the indicator travelling through the heart chambers [17]. The equation is given in the legend of Supplementary data, Figure S1. Total ejection fraction (TEF, %) was calculated from the stroke volume ($SV = CO/HR$) and TEDV according to the formula $TEF = 100 \cdot \frac{4 \cdot SV}{TEDV}$ [18]. Both TEDV and TEF cannot discriminate between right and left heart compartments and represent a composite parameter of right and left heart systolic and diastolic function.

At the beginning of the HD session, fluid status was determined using bioimpedance spectroscopy (body composition monitor; Fresenius Medical Care, Homburg, Germany). Overhydration (OH) was inferred from the body composition model that divides the whole body into three compartments, i.e. normally hydrated lean tissue, normally hydrated adipose tissue

Table 1. Baseline characteristics of the cohort (n = 215)

Variable	Value
Age, median (interquartile range) (years)	73 (64–80)
Gender distribution (%)	
Female	35
Male	65
Body weight (kg)	77 (69–88)
Time on dialysis, months	47 (20–83)
Dialysis access (%)	
Native AV fistula	85
PTFE graft	15
Site of dialysis access (%)	
Upper arm	65
Lower arm	34
Underlying renal disease (%)	
Diabetic nephropathy	20
Glomerulonephritis	20
Hypertensive nephropathy	7
PKD	5
Unknown	48
Residual excretion (L/24 h)	0.3 (0–1.2); 52% anuric
Ultrafiltration (L/session)	2.1 (1.3–2.8)
Ultrafiltration rate (mL/h/kg)	6.5 (3.8–8.7)
Dialyser (%)	
High flux	98
Low flux	2
Dialysis modality	31% double-needle HD, 69% OL-HDF with substitution volume 21 (18–24) L
Blood pump speed, mL/min	300 (280–320)
Dialysate temperature (°C)	36.5
Dialysate Na/K/Ca	138 (136–139) mM/2 (2–3) mM/1.5 (1.25–1.5) mM
Dialysis duration (h)	4 (4–4.25)
spKt/V	1.5 (1.3–1.7)
Cardiac comorbidity (%)	
Valvular disease	47
LV hypertrophy	43
CAD	35
PTCA	24
Pulmonary hypertension	22
Pacemaker	7
Systolic LV function from echocardiography (%)	
Normal	63
Slightly reduced	11
Moderate reduction	6
Severe reduction	2
Unknown	18
Medication (%)	
Phosphate binders	85 (n=183)
Vitamin D replacement	98 (n=211)
ACE-I or ARB	63 (n=135)
Beta-blockers	69 (n=148)
Calcium channel blockers	41 (n=103)
Nitrates	9 (n=23)
Statins	35 (n=88)
Erythropoietin (I.E./week)	4000 (0–9000)

Values are shown as median and interquartile range for continuous variables and as percentages for categorical variables.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PTFE, polytetrafluorethylene; PKD, polycystic kidney disease; CAD, coronary artery disease; PTCA, percutaneous coronary angioplasty; OL-HDF, online haemodiafiltration.

and OH [19, 20]. Blood pressure (BP) and heart rate (HR) were taken at the measurement of CO using the sphygmomanometer of the HD machine (5008, Fresenius Medical Care).

Laboratory assays and clinical data

From each patient, one sample was taken at the beginning of the HD session in which haemodynamics were measured. Plasma concentration of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was measured using an automated Siemens Immulite XPT solid-phase chemiluminescent immunoassay system (Siemens Healthcare Diagnostics, Eschborn, Germany). From each patient, data on residual diuresis (measured by 24 h urine collection), single-pool *Kt/V* (mean of last four values), interdialytic weight gain, dialysis access and membrane and time on dialysis were extracted. The systolic left ventricular (LV) function was classified from available echocardiography examinations that mainly relied on visual impression that is prone to inter- and intra-observer variability [21]. Adverse events were defined as cramps, syncope, bradycardia, chest pain, dyspnoea and problems with the vascular access.

Statistical analysis

The primary endpoint of the study was the quantification of haemodynamic parameters and their intradialytic changes as assessed in a cross-sectional approach during a single HD session. Another endpoint was their association with mortality (both all-cause and cardiovascular) in a prospective design. Secondary endpoints were all other correlations and performance of bioimpedance spectroscopy and NT-pro-BNP. Echocardiographic data were not included in the analyses as these were not collected in a comprehensive and standardized manner. All continuous data were checked for normal distribution using the Kolmogorov–Smirnov test. Differences between the values before and after HD were tested with Wilcoxon signed-rank test. The association of the variables with clinical- or dialysis-related factors was analysed using non-parametric correlation. To identify independent determinants of Δ CI, multivariable linear regression analyses were performed. Log-transformed variables entering multivariable linear regression were selected by a stepwise approach (enter when $P < 0.2$, remove when $P > 0.21$). The follow-up period started on the day of study and lasted until 30 April 2017. Causes of death were classified according to the best knowledge of each particular case. Cardiovascular death was considered as sudden death (most probably circulatory or cardiac arrest) and death due to a cardiovascular event or disease (coronary artery disease, heart failure, stroke and peripheral artery disease). Patients receiving a kidney graft were censored on the day of transplantation. Values of the deceased patients were compared with those from the surviving patients using a *t*-test. Kaplan–Meier curves were generated after stratification into tertiles of the variable according to its distribution. Survival curves were compared using the log-rank test. Crude and adjusted proportional hazards were calculated using the Cox regression analysis. Statistical analyses were done with MedCalc Statistical Software version 17.4.4 (MedCalc Software bvba, Ostend, Belgium) and JMP 11 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study cohort

Of the 235 patients who were treated with an AV fistula or graft in the participating centres, 215 were included in the

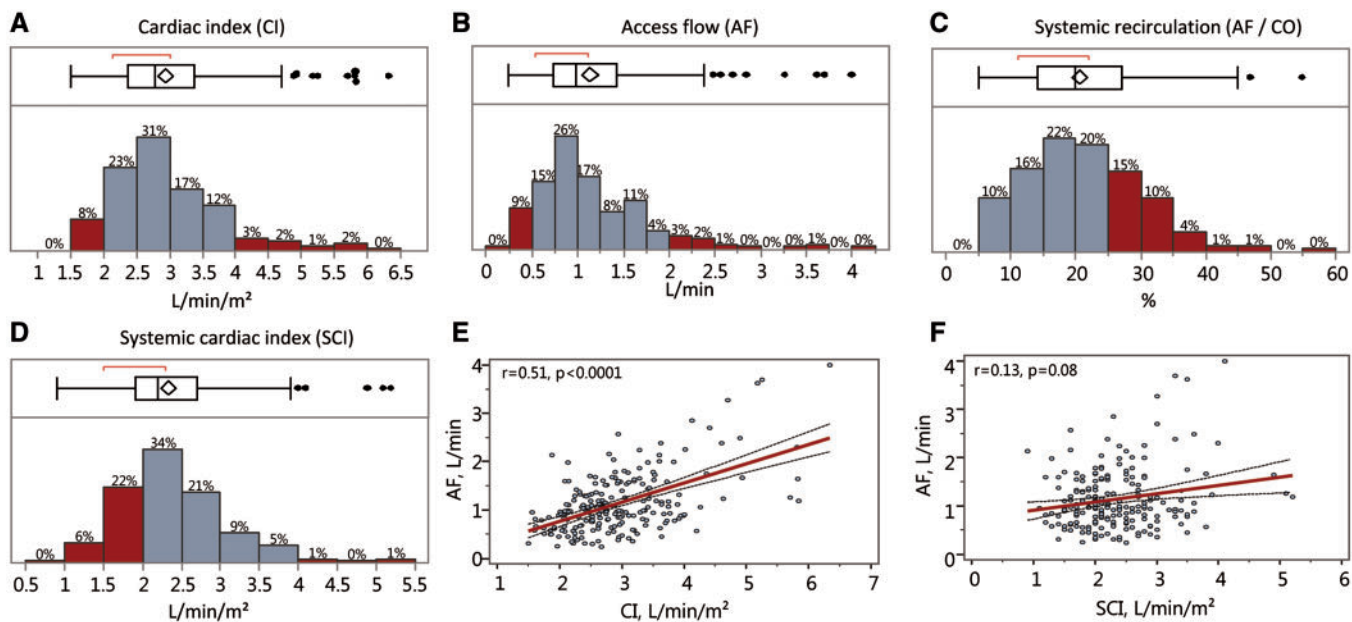


FIGURE 1: Distribution of (A) CI, (B) AF, (C) AF/CO and (D) SCI in the cohort and correlation of CI and SCI with AF (E, F). A significant proportion of patients (red bars) have high or low CI, AF, AF/CO and SCI.

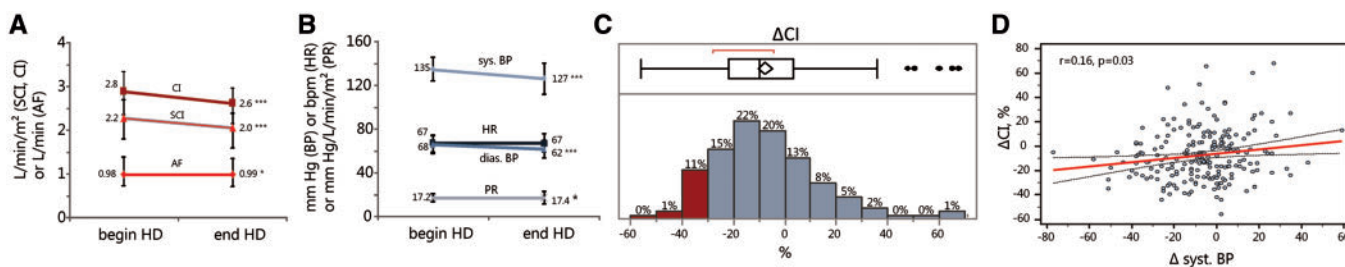


FIGURE 2: Changes of CI and other haemodynamic parameters during HD (A, B), distribution of Δ CI (C) and correlation of Δ CI with Δ systolic BP (D). HD leads to reduction of CI, whereas AF remains constant and as a result SCI falls (A). Systolic and diastolic BP falls as well, whereas HR remains constant. PR increased as part of counterregulation.

study. Five patients declined to participate. Fifteen patients were excluded due to a stenosed access defined by recirculation. The characteristics of the study cohort are provided in Table 1. Participants had a median age of 73 years and had been dialysed for a median of 47 months using a native AV fistula (85%) and a high-flux membrane (98%). Online haemodiafiltration (HDF) was used in $n = 144$ (69%) with a high-substitution volume (median 21 L). Cardiac comorbidities were present in a large proportion of the patients. Valvular disease was the most frequent condition (47%). Systolic LV dysfunction was found in 19% of the patients (Table 1).

Mean values and distribution of haemodynamic parameters

Mean CO, CI and AF were 5.2 L/min (interquartile range 4.5–6.4), 2.8 L/min/m² (2.4–3.4) and 980 mL/min (742–1415), respectively, each measured at the beginning of HD. Eight per cent of the patients had high CI (>4 L/min/m²), whereas 8% had low CI (<2 L/min/m²) (Figure 1A). AF >2000 mL/min was found in 7% of the patients (Figure 1B). AF/CO exceeding 20, 25 and 30% indicating risk for high-output cardiac failure [22] was found in 51, 31 and 16%,

respectively, of the patients (Figure 1C). Mean SCI that is calculated from the difference of CI and AF was 2.2 L/min/m² (1.9–2.7), and <2 L/min/m² in 28% of the patients (Figure 1D). AF and CI, but not SCI, were strongly correlated to each other, suggesting that AF increases CI in HD patients (Figure 1E and F). Other correlations of the haemodynamic parameters are shown in Supplementary data, Table S1. OH determined from bioimpedance spectroscopy highly correlated with CBVI, TEDVI and NT-pro-BNP. NT-pro-BNP strongly correlated with TEDVI and TEF, but not with CI, AF or SCI (Supplementary data, Table S1).

Changes of haemodynamic parameters during HD

At the end of HD, CI and AF significantly fell by –10% (–22 to 3, $P < 0.0001$) and –4% (–13 to 5, $P = 0.0004$), respectively (Figure 2A). CBVI fell by –9% (–23 to 3, $P < 0.0001$). PR increased slightly by +3% (–9 to 21, $P = 0.01$) and BP fell by –7/–4 mmHg to 128/63 mmHg ($P < 0.0001$, Figure 2B). For 28% of the patients, CI fell by >20% and was associated with a drop in systolic BP of >9 mmHg (Figure 2C). Δ CI (%) only weakly correlated with Δ BP ($r = 0.16$; $P = 0.03$, Figure 2D). There was no significant difference of Δ CI between

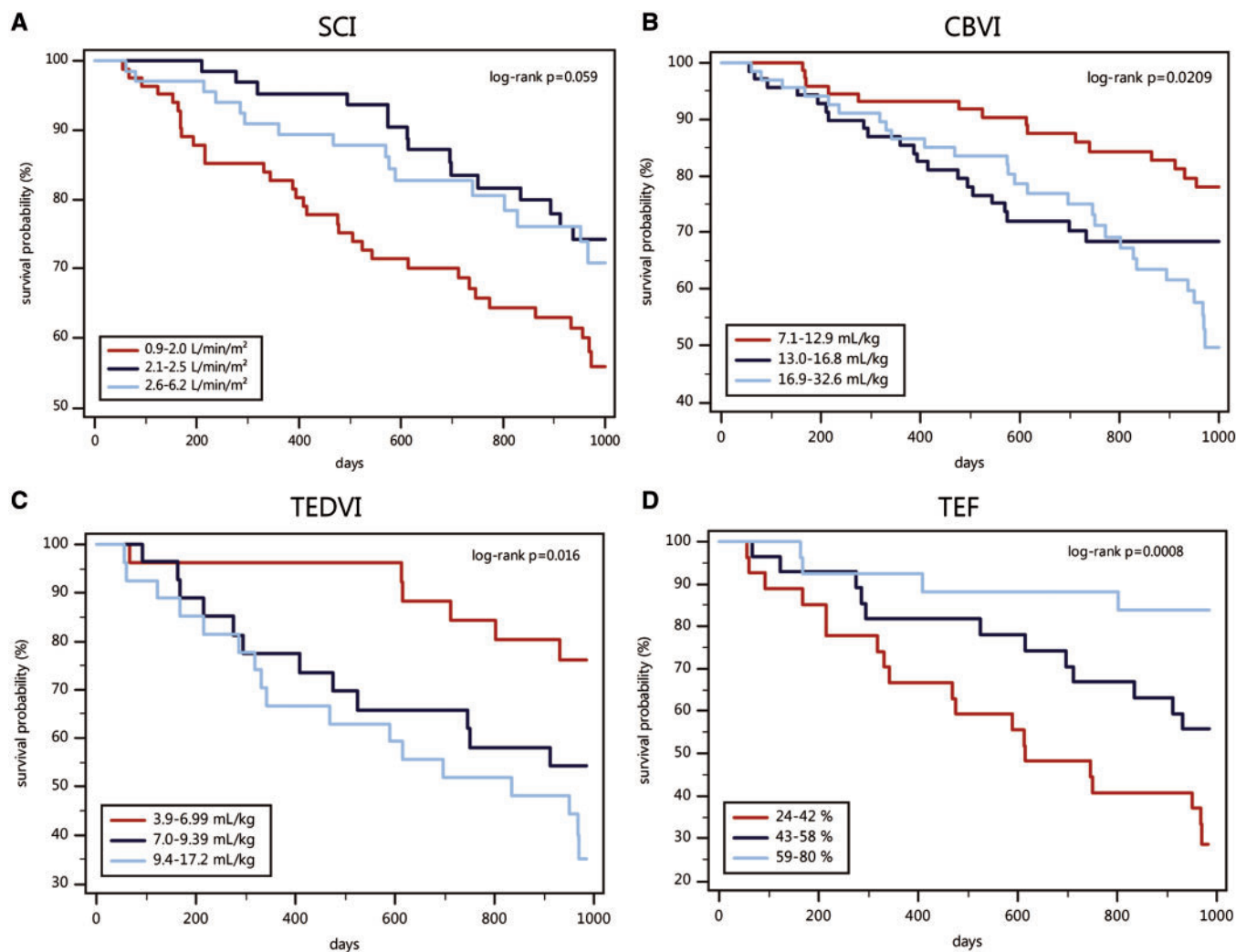


FIGURE 3: Survival curves for tertiles of SCI (A), CBVI (B), TEDVI (C) and TEF (D). Patients in the lowest tertiles of SCI and TEF as well as in the highest tertiles of CBVI and TEDVI have reduced survival. Note that TEF has the best separation between the tertiles and the greatest amplitude.

Table 2. Haemodynamic parameters at the beginning and at the end of HD

Parameter	n	Begin	End	P-value
CO (L/min)	215	5.20 (4.52–6.40)	4.75 (4.09–5.78)	<0.0001
SV (mL)	213	78 (66–95)	72 (57–90)	<0.0001
HR (bpm)	215	67 (60–75)	67 (59–75)	0.9865
AF/CO (%)	215	20 (14–27)	21 (15–28)	0.0010
CBVI (mL/kg)	213	15.0 (11.9–18.1)	13.4 (10.0–16.4)	<0.0001
TEDVI (mL/kg)	79	8.0 (6.5–10.1)	7.3 (5.7–9.6)	0.0007
TEF (%)	79	48 (39–61)	49 (39–61)	0.8145

Values are shown as medians with interquartile range. P-value from paired Wilcoxon's rank-sum test. Bonferroni-corrected significance level set to 0.0071.

patients treated with HDF [−8 (−24 to 3), $n = 144$] and HD [−10 (−21 to 3), $n = 71$]. Values from the beginning to the end of HD from all other haemodynamic parameters are shown in Table 2. Correlations of the changes of the haemodynamic parameters are shown in Supplementary data, Table S2. The decrease in CI was paralleled by decreases in AF and TEDVI and a counterregulatory increase in PR but not HR (Supplementary data, Table S2). The latter was not correlated with beta-blocker use ($P = 0.98$). Similarly, treatment with antihypertensive drugs

such as angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and calcium antagonist had no influence on Δ CI and Δ PR. Multivariable regression was utilized to detect independent predictors of Δ CI. As shown in Table 3, high age, high CI and high ultrafiltration rate were independently associated with a fall in CI, whereas high AF, OH and PR were protective.

Adverse events such as cramps, syncope, bradycardia, chest pain, dyspnoea and problems with the vascular access occurred

Table 3. Multivariable linear regression model for predicting CI fall (Δ CI)

Independent variables	Coefficient	Standard error	r_{partial}	P-value	VIF
(Constant)	2.3463				
UFR (log mL/h/kg)	-0.07689	0.0099	-0.4761	<0.0001	1.137
CI at begin (log L/m ²)	-0.2426	0.0956	-0.1736	0.0119	4.704
Diastolic BP (log mmHg)	-0.1522	0.0809	-0.1297	0.0613	1.822
Age (log years)	-0.2178	0.0664	-0.2226	0.0012	1.370
PR at begin (log mmHg/L/m ²)	0.2174	0.0894	0.1666	0.0159	4.483
AF at begin (log L/m ²)	0.1097	0.0259	0.2824	<0.0001	1.316
OH (log L/m ²)	0.3007	0.0594	0.3322	<0.0001	1.200

Linear regression model with Δ CI in % of the baseline value as dependent variable. Variables were entered after log transformation and a stepwise approach with $P < 0.2$. Adjusted $r^2 = 0.3516$, $n = 215$.

VIF, variation inflation factor; UFR, ultrafiltration rate.

Table 4. C-statistics of the prognostically relevant parameters for all-cause mortality

Parameter	AUC	95% CI	P-value	Cut-off	Sensitivity (%)	Specificity (%)
SCI (L/min/m ²)	0.601	0.532–0.667	0.0213	<1.9	42	77
CBVI (mL/kg)	0.588	0.519–0.655	0.0388	>12.9	77	40
TEDVI (mL/kg)	0.720	0.610–0.814	0.0002	>7.7	74	64
TEF (%)	0.774	0.668–0.859	<0.0001	<50.4	86	62
OH (L/m ²)	0.643	0.575–0.707	0.0003	>0.4	92	33
NT-pro-BNP (pg/mL)	0.667	0.599–0.729	<0.0001	>3521	82	51

All-cause mortality occurred in $n = 65$ (30% of the cohort). TEDVI and TEF was analysed in a subgroup ($n = 82$) with all-cause mortality occurring in $n = 35$ (43%) of the patients. Only values from the beginning of HD were analysed.

Table 5. Hazard ratios for all-cause mortality from Cox regression

Parameter	SD	Crude		Adjusted ^a	
		Hazard ratio with 95% CI	P-value	Hazard ratio with 95% CI	P
SCI (L/min/m ²)	0.70	0.78 (0.58–1.03)	0.0900	1.03 (0.74–1.43)	0.8456
CBVI (mL/kg)	6.29	1.28 (1.00–1.64)	0.0514	1.17 (0.87–1.58)	0.3022
TEDVI (mL/kg)	2.54	1.51 (1.15–1.90)	0.0031	1.62 (1.13–2.32)	0.0084
TEF (%)	14.86	0.48 (0.32–0.70)	0.0002	0.57 (0.36–0.91)	0.0194
NT-pro-BNP (pg/mL)	14 703	1.44 (1.21–1.71)	<0.0001	1.47 (1.22–1.77)	0.0001
OH (L/m ²)	0.87	1.43 (1.14–1.78)	0.0018	1.53 (1.17–2.02)	0.0023

All-cause mortality occurred in $n = 65$ (30%) of the patients. $n = 150$ alive patients were censored. The Hazard ratios with 95% CI are displayed for an increase by 1 SD of the parameters. Only values from the beginning of HD were analysed.

^aAdjusted for other factors associated with increased mortality in this cohort such as age, gender, body mass index, time on dialysis, vascular access (fistula/graft), flux (low/high), plasma albumin and inorganic phosphorus concentration, and presence of peripheral artery disease.

in 69 patients (32%) during the HD session and the previous 3 months. There was no difference in the Δ CI of these patients [-8 (-20 to 7)] and of those without adverse events [-11 (-24 to -1), $P = 0.26$]. Furthermore, there was no significant correlation between adverse events and all other haemodynamic parameters (CI, SCI, AF, TEDVI, TEF and their changes, data not shown).

Prognostic value of haemodynamic parameters

After 2.6 years, 65 patients had died (30%), 8 (4%) received kidney transplantation and 7 (3%) moved away or terminated HD. The mean follow-up time was 963 days (575–983 days). Cardiovascular death as defined by a composite of sudden death, coronary artery disease, stroke and peripheral artery disease occurred in 25 patients (38% of all deaths). The remaining causes of death were malignoma (8 patients, 12%), infection

(8 patients, 12%), gastrointestinal bleeding (4 patients, 6%), discontinuation (8 patients, 12%) and unknown (12 patients, 18%). The comparison of the median values of the haemodynamic parameters between survivors and deceased patients is shown in [Supplementary data, Table S3](#). Deceased patients had significantly reduced SCI and TEF, hypervolaemia (OH, CBVI and TEDVI) and increased NT-pro-BNP. [Figure 3](#) shows survival curves for tertiles of SCI, CBVI, TEDVI and TEF. The separation of the tertiles was best for TEF, followed by TEDVI.

The c-statistics of the prognostically relevant haemodynamic parameters for all-cause and cardiovascular mortality are shown in [Table 4](#) and [Supplementary data, Table S4](#). Among the tested parameters, TEF had the highest AUC value, followed by TEDVI, CBVI and SCI. AUC values of all-cause and cardiovascular mortality were in parallel. Finally, hazard ratios from Cox regression analysis were calculated in a crude and adjusted

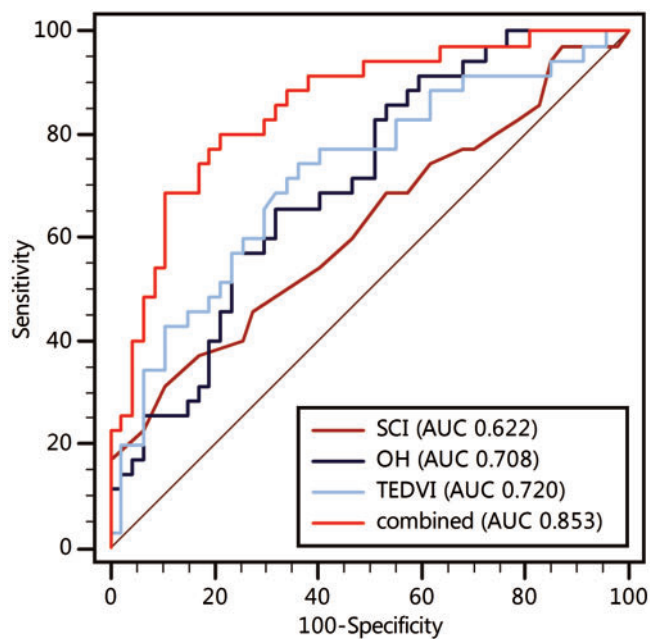


FIGURE 4: Receiver-operating characteristic curves for the outcome all-cause mortality by TEDVI, SCI, OH and the combination of these three parameters. The combined model was derived from logistic regression yielding the formula

$$\text{logit}(p) = -1.04 - 2.12 \cdot \text{SCI} \text{ (L/min/m}^2\text{)} + 1.18 \cdot \text{OH} \text{ (L/1.73m}^2\text{)} + 0.50 \cdot \text{TEDVI} \text{ (mL/kg)},$$

whereby p denotes the risk for all-cause mortality. Note that the AUC for the combination of the parameters was significantly higher than the AUC for each single parameter (P-value between 0.0005 and 0.0116). The cut-off value of the combination was 0.59 and had a sensitivity and specificity of 80 and 79%, respectively.

model. Hazard ratios for TEDVI and TEF were strong and independent predictors of all-cause mortality similar to OH and NT-pro-BNP (Table 5). Owing to the low number of CV deaths less robust results were obtained when Cox regression was repeated with cardiovascular mortality as the endpoint (Supplementary data, Table S5).

To find parameters independently associated with all-cause mortality that could be summarized into a composite risk score, a logistic regression with a stepwise approach was performed. Among all of the parameters listed in Table 4, three parameters were highly independent predictors of mortality and could be combined in a multivariable logistic regression model: TEDVI ($P = 0.0012$), SCI ($P = 0.0004$) and OH ($P = 0.0033$). Using a calculated score derived from these parameters, the c-statistics could be improved up to 0.853 (0.757–0.921), a value statistically higher than the respective value derived from single parameters (P-value between 0.0005 and 0.0116; Figure 4).

DISCUSSION

This is the first study to collect comprehensive data on systemic haemodynamics during HD in a large cohort of stable HD patients. Furthermore, we present data on the prognostic relevance of the studied parameters which, up to now, have been entirely unknown. The main findings of the study are that HD leads to a

fall in CI in the majority of the patients while AF remains constant, thus resulting in a fall in SCI, a measure that describes the effective perfusion to the whole body. Besides a low baseline systolic BP, the fall in CI is independently explained by high ultrafiltration volume leading to reduced preload (evidenced by low CBVI and TEDVI) and is blunted by OH, high baseline PR and AF. Of note, patients did not compensate with an increase in HR, regardless of beta-blocker use, which suggests chronotropic incompetence. The intradialytic changes in haemodynamics were in agreement with previous smaller studies [23–25].

In the absence of CI measurements, clinicians frequently rely on BP changes to assess CI. From a haemodynamic perspective, BP is the driving force for CI and determines CI as a function of PR. Therefore, BP cannot be a substitute for CI. Our data show that BP and CI correlate poorly and that BP changes do not reflect changes in CI adequately and sensitively as previously reported [26]. Therefore, only a direct measurement of CI (e.g. using ultrasound dilution) can fill this gap. So far, there is a lack of studies with repeat CI measurements during HD using ultrasound dilution. In a recent study, repeat CI measurements were performed during HD using magnetic resonance imaging and demonstrated a continuous fall in CI from 3.6 to 2.6 L/min/m² (corresponding to –28%) by the end of HD [27]. In that study, there was no difference between HD and HDF, which agreed with our study. The authors found a reduction of myocardial perfusion leading to myocardial stunning that might be another cause of a fall in CI besides ultrafiltration and reduced preload. Surprisingly, we could not find any association of Δ CI with adverse events. However, this finding applies only for a CI fall of maximally –56% occurring continuously over a 4-h HD session. It is beyond doubt that abrupt and more dramatic falls in CI might lead to adverse events and symptoms that could occur during shorter HD sessions with high ultrafiltration rates exceeding 10 mL/h/kg, as reported by the study of Flythe *et al.* [28].

The clinical relevance of the haemodynamic parameters became evident when analysing their prognostic significance and association with mortality. We found that a low baseline SCI was associated with mortality, but not CI. This can be explained by the fact that SCI reflects whole-body perfusion more adequately than CI and that high AF can pretend normal CI. Interestingly, a fall in CI or SCI during HD was not associated with mortality at all. This seems counterintuitive given the association of a fall in CI with myocardial stunning, evidenced by regional wall motion abnormalities (RWMAs) as recently shown in an MR study [27], and the association of stunning with mortality as published by the same group previously [29]. Unfortunately, we have not recorded any measure of myocardial stunning in our study. Arguing that TEF or its change might reflect RWMA, we have found that TEF was not depressed at the end of HD in the majority (90%) of the patients and that Δ TEF was not associated with mortality. More studies are required to clarify the association among Δ CI, myocardial stunning and mortality.

In the present study, TEF at the beginning of HD emerged as the most robust marker of increased mortality, followed by TEDVI and CBVI. One reason for this might be the exact determination of TEF with high resolution that appears to be as exact as ejection fraction determination from MR [30]. In the study

[26], the cut-off value for increased mortality was LVEF <50%, which is identical to the cut-off from our receiver operating characteristic curve analysis. TEF cannot distinguish between right ventricular ejection fraction (RVEF) and/or LVEF and reflects the combination of RVEF and LVEF, both of which are important and independent determinants of CI. In an MR study, LVEF had a moderate correlation to RVEF ($r=0.40$), and a considerable proportion of patients (37%) had low LVEF <35% with preserved RVEF and vice versa (56% of the patients) [31]. Thus, reduced TEF can be regarded as a composite parameter of both right ventricular and LV dysfunction that might explain its excellent prognostic performance.

Although CI, SCI and TEF reflect systolic function, TEDVI relates to ventricular filling during diastole. We have found that TEDVI and CBVI were reduced by HD owing to ultrafiltration. On the contrary, increased TEDVI and CBVI at baseline predicted mortality indicating increased ventricular filling and pulmonary congestion. TEDVI shows similarity to the LV end-diastolic pressure, an established parameter of ventricular filling and mortality in patients with LV dysfunction [32, 33]. It is remarkable that both TEF and TEDVI, but not CI and SCI, were strongly correlated to the cardiac biomarker NT-pro-BNP, indicating that TEF and TEDVI reflect haemodynamic changes associated with NT-pro-BNP release and increased mortality.

Surprisingly, we did not observe patients at risk for high-output heart failure with increased AF and AF/CO [22]. This might be due to the low number of patients in these strata (<10%) resulting in a low statistical power. Also, high AF was not correlated with the prognostically relevant parameters TEF and NT-pro-BNP. Therefore, AF of 1 L/min or slightly higher seems to be compensated by most of the HD patients. However, in our practice, patients with known heart failure are more likely to start HD with a dialysis catheter, thus introducing a bias.

There are some limitations of the study that merit discussion. The presented data applies strictly speaking only for patients with AV fistulae or grafts, but not for patients with a dialysis catheter. The latter subgroup is often sicker and has a higher incidence of cardio-renal syndrome. As a consequence, haemodynamics and responses to HD and ultrafiltration might be different and much more pronounced. The fact that we could not find any correlation of adverse events with changes in CI might be the result of a lack of haemodynamic data taken more frequently during the course of HD. Still, prognostic significance was best with the values taken at the beginning of HD. In addition to a one-time measurement, it would also be important to study the variability and longitudinal changes to better define the association of haemodynamic parameters with clinical endpoints and mortality. It must be noted that haemodynamic monitoring may differ according to the technology and methodology used [34]. However, ultrasound dilution appears to be a gold standard in comparison with others [35, 36].

Haemodynamic monitoring provides a unique data set to gain insight into the haemodynamic profile of an individual HD patient with regard to cardiac performance, congestion and compensation of AF (indicated by AF/CO). It also allows the identification of patients at increased mortality risk using TEF, which promises to be a robust risk marker that could be implemented for repeated monitoring of HD patients. While cardiac

biomarkers represent static risk markers, many of the haemodynamic parameters are amenable to treatment that, in turn, could improve HD treatment and most importantly prognosis of HD patients. Another advantage of haemodynamic monitoring is the fact that it is directly carried out by the dialysis team without the need for external resources or referrals.

In conclusion, this study shows that HD leads to a reduction of CI due to ultrafiltration and reduced preload. Haemodynamic monitoring identifies a significant number of HD patients with cardiac impairment who are at risk for increased mortality. Among the parameters, TEF and TEDVI were the most powerful single predictors. The data underscore the utmost importance of cardiac function for the prognosis of HD patients.

SUPPLEMENTARY DATA

Supplementary data are available at ndt.oup.com.

ACKNOWLEDGEMENTS

We thank Dr Nikolai Krivitski for some suggestions to the study protocol.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32 (Suppl 3): S112–S119
2. de Jager DJ, Grootendorst DC, Jager KJ *et al*. Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA* 2009; 302: 1782–1789
3. Jager KJ, Lindholm B, Goldsmith D *et al*. Cardiovascular and noncardiovascular mortality in dialysis patients: where is the link? *Kidney Int Suppl* 2011; 1: 21–23
4. Zoccali C, Benedetto FA, Mallamaci F *et al*. Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. *J Am Soc Nephrol* 2004; 15: 1029–1037
5. Yamada S, Ishii H, Takahashi H *et al*. Prognostic value of reduced left ventricular ejection fraction at start of hemodialysis therapy on cardiovascular and all-cause mortality in end-stage renal disease patients. *Clin J Am Soc Nephrol* 2010; 5: 1793–1798
6. Herzog CA, Asinger RW, Berger AK *et al*. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011; 80: 572–586
7. Passman R, Herzog CA. End-stage renal disease: sudden cardiac death: stratifying risk in dialysis patients. *Nat Rev Nephrol* 2011; 7: 133–135
8. Artunc F, Mueller C, Breidhardt T *et al*. Sensitive troponins—which suits better for hemodialysis patients? Associated factors and prediction of mortality. *PLoS One* 2012; 7: e47610
9. Artunc F, Mueller C, Breidhardt T *et al*. Comparison of the diagnostic performance of three natriuretic peptides in hemodialysis patients: which is the appropriate biomarker? *Kidney Blood Press Res* 2012; 36: 172–181
10. Artunc F, Nowak A, Muller C *et al*. Mortality prediction using modern peptide biomarkers in hemodialysis patients—a comparative analysis. *Kidney Blood Press Res* 2014; 39: 563–572
11. Krivitski NM. Theory and validation of access flow measurement by dilution technique during hemodialysis. *Kidney Int* 1995; 48: 244–250
12. Krivitski NM. Novel method to measure access flow during hemodialysis by ultrasound velocity dilution technique. *ASAIO J* 1995; 41: M741–M745
13. Krivitski NM, Depner TA. Cardiac output and central blood volume during hemodialysis: methodology. *Adv Ren Replace Ther* 1999; 6: 225–232
14. Kisloukhine VV, Dean DA. Validation of a novel ultrasound dilution method to measure cardiac output during hemodialysis. *ASAIO J* 1996; 42: M906–M907

15. Nikiforov YV, Kisluchine VV, Chau NI. Validation of a new method to measure cardiac output during extracorporeal detoxification. *ASAIO J* 1996; 42: M903–M905
16. Tucker TNS, Smith I, Lasseter P *et al.* Unrecognized deterioration of cardiac function during hemodialysis. *J Am Soc Nephrol Abstracts* 2002; 13: 267A
17. Krivitski NM, Kislukhin VV, Thuramalla NV. Theory and in vitro validation of a new extracorporeal arteriovenous loop approach for hemodynamic assessment in pediatric and neonatal intensive care unit patients. *Pediatr Critical Care Med* 2008; 9: 423–428
18. Dobson A, Kislukhin VV. Heart blood volume by dilution in patients on hemodialysis. *ASAIO J* 2004; 50: 278–284
19. Chamney PW, Wabel P, Moissl UM *et al.* A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am J Clin Nutr* 2007; 85: 80–89
20. Moissl UM, Wabel P, Chamney PW *et al.* Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas* 2006; 27: 921–933
21. Johri AM, Picard MH, Newell J *et al.* Can a teaching intervention reduce interobserver variability in LVEF assessment: a quality control exercise in the echocardiography lab. *JACC Cardiovasc Imaging* 2011; 4: 821–829
22. Basile C, Lomonte C, Vernagione L *et al.* The relationship between the flow of arteriovenous fistula and cardiac output in haemodialysis patients. *Nephrol Dial Transplant* 2007; 23: 282–287
23. Prakash S, Reddan D, Heidenheim AP *et al.* Central, peripheral, and other blood volume changes during hemodialysis. *ASAIO J* 2002; 48: 379–382
24. Hoeben H, Abu-Alfa AK, Mahnensmith R *et al.* Hemodynamics in patients with intradialytic hypotension treated with cool dialysate or midodrine. *Am J Kidney Dis* 2002; 39: 102–107
25. Krivitski NM, MacGibbon D, Gleed RD *et al.* Accuracy of dilution techniques for access flow measurement during hemodialysis. *Am J Kidney Dis* 1998; 31: 502–508
26. Pandeya S, Lindsay RM. The relationship between cardiac output and access flow during hemodialysis. *ASAIO J* 1999; 45: 135–138
27. 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: 1269–1277
28. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int* 2011; 79: 250–257
29. Burton JO, Jefferies HJ, Selby NM *et al.* Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009; 4: 914–920
30. Klem I, Shah DJ, White RD *et al.* Prognostic value of routine cardiac magnetic resonance assessment of left ventricular ejection fraction and myocardial damage: an international, multicenter study. *Circ Cardiovasc Imaging* 2011; 4: 610–619
31. Jimenez-Juan L, Karur GR, Connelly KA *et al.* Relationship between right and left ventricular function in candidates for implantable cardioverter defibrillator with low left ventricular ejection fraction. *J Arrhythm* 2017; 33: 134–138
32. Bagai A, Armstrong PW, Stebbins A *et al.* Prognostic implications of left ventricular end-diastolic pressure during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: findings from the Assessment of Pexelizumab in Acute Myocardial Infarction study. *Am Heart J* 2013; 166: 913–919
33. Mielniczuk LM, Lamas GA, Flaker GC *et al.* Left ventricular end-diastolic pressure and risk of subsequent heart failure in patients following an acute myocardial infarction. *Congest Heart Failure* 2007; 13: 209–214
34. Bunz H, Narushima L, Heyne N *et al.* Evaluation of a non-invasive continuous hemodynamic monitoring device (ICON) in hemodialysis patients. In: *Abstract at the 9th Annual Meeting of the German Society for Nephrology, Mannheim, 2017*, <http://www.abstractserver.com/publication/nephro2017/nephro2017Abstracts.PDF>
35. Lopot F, Portova M, Bednarova L *et al.* Vascular access quality monitoring. *EDTNA ERCA J* 2003; 29: 77–84
36. Garland JS, Moist LM, Lindsay RM. Are hemodialysis access flow measurements by ultrasound dilution the standard of care for access surveillance? *Adv Ren Replace Ther* 2002; 9: 91–98

Received: 22.11.2017; Editorial decision: 31.1.2018