ORIGINAL ARTICLE

Effect of hemodialysis on impedance cardiography (electrical velocimetry) parameters in children

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Abstract

Background Pediatric hemodialysis (HD) patients have a high incidence of cardiovascular morbidity and mortality. The study aim was to investigate whether impedance cardiography (electrical velocimetry, EV) is suitable as a hemodynamic trend monitoring tool in pediatric patients during HD.

Methods Measurements by EV were obtained before, during, and after HD in a prospective single-center pediatric observational study. In total, 54 dialysis cycles in four different pediatric patients with end-stage kidney disease on chronic HD were included. EV parameters analyzed were heart rate (HR), stroke volume (SV), stroke volume index (SI), cardiac output (CO), cardiac index (CI), thoracic fluid content (TFC), index of contractility (ICON), stroke volume variation (SVV), variation of ICON (VIC), R-R interval (TRR), pre-ejection period (PEP), left ventricular ejection time (LVET), and systolic time ration (STR). Systemic vascular resistance index (SVRI) was calculated.

Results EV did measure significant changes in cardiovascular parameters associated with HD. The following parameters increased after HD: HR (9%), SVV (19%), VIC (33%), PEP (8%), and STR (18%). A decrease after HD was measured in SV (18%), SI (18%), CO (10%), CI (10%), TFC (10%), ICON (7%), TRR (7%), LVET (8%), and LVET (8%). SVRI was not affected by HD. The changes were correlated to ultrafiltration. HD cycles without fluid withdrawal also altered cardiovascular parameters.

Conclusions Pediatric HD with and without fluid withdrawal changes hemodynamic EV monitoring parameters. Possibly EV may be useful to optimize HD management in pediatric patients.

Keywords Impedance cardiography · Pediatrics · Renal failure · Hemodialysis · Cardiac index · Fluid status

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Introduction

Pediatric hemodialysis patients have a high incidence of cardiovascular morbidity and mortality [1, 2]. Therefore an optimized intradialytic hemodynamic monitoring for this patient group appears desirable.

Bioimpedance and impedance cardiography [3, 4] is based on the human body properties as a resistor to an applied high-frequency AC voltage. This resistance depends on the patient's body composition and fluid status [5–7]. Body resistance alterations during cardiac cycle can be used to calculate left ventricular stroke volume and cardiac output [4]. Impedance cardiography monitors are commercially available. In this study, an impedance cardiography device based on the algorithm of electric velocimetry (EV) [4] was used. Although impedance cardiography has been known for several decades [8], it has not yet found widespread clinical use. Depending on study design and the studied patient

groups, there is conflicting evidence with moderate or poor concordance between impedance cardiography and reference CO monitoring methods, e.g., in congenital heart disease or heterogenic adult patient groups [9–14]. Some studies on more homogenous adult [15] and pediatric patient groups [16–19] did show good correlation and even formal concordance [20] for EV with reference methods. Trend-following characteristics of EV have been assessed in very few studies [12, 16–19, 21–23] including studies on animal models [24, 25]. Human literature data on EV trend following have been published on neonates [17, 19, 22] under different circumstances, i.e., transition at birth [23], with congenital heart disease [16, 18], or persistent arterial duct [22] as well as on children [19] and adults, e.g., during liver transplantation [12] or during HD [26]. A recent meta-analysis [27] on the comparison between EV and other monitoring methods did show a reasonably low bias, but high mean percentage error equivalent to a low precision of the measurements. Based on literature data [15–27], a correlation between EV and reference methods may be assumed, even though EV is not interchangeable with other methods.

Hemodialysis (HD) causes a defined alteration in a patient's fluid status. An HD cycle with fluid withdrawal can be considered as the opposite of a fluid bolus administration with corresponding effects on circulation. In general, HD may result in a reduced ventricular filling and subsequently lower stroke volume and cardiac output during HD. Effects of HD on SV or CI have been demonstrated using different monitoring methods in more historic [28, 29] and in recent publications [26, 30–34]. A recent adult study did show a stroke volume change in the same direction under HD comparing impedance cardiography to echocardiography [26]. The patient's physiological response to HD – e.g., increase in heart rate (HR) and/or increase in systemic vascular resistance index (SVRI) – is targeted to maintain sufficient blood pressure and body perfusion. If the response is inadequate, intradialytic hypotension may occur [34].

Evaluation of a (new) monitoring method includes validation in comparison to reference methods [15–27]. The monitoring method should be accurate and precise and have a suitable trend-following ability [35]. This should be true also for the patient group for whom use of the method is intended. Finally, application of a new method should result in a diagnostic [36] or prognostic benefit, i.e., based on goal-directed therapy [37]. To our knowledge, published data on goal-directed therapy based on EV do not exist for the pediatric age group. For adults, an intratracheal bioimpedance method (not EV) has been used to guide treatment in coronary heart surgery [37].

This study aims to evaluate whether the monitoring method EV is capable to detect intradialytic circulatory changes associated with HD in pediatric patients. Thus the study evaluates the trend-following capability of EV as a monitoring tool under the condition of pediatric HD.

Methods and patients

Subjects

In a prospective single-center observational study at the University Medical Center Hamburg-Eppendorf, pediatric patients with chronic kidney disease on HD were included. The study was approved by the local ethics board. Informed parental consent was obtained. The mean patient age was 12.29 years (range 5.66–13.98 years). In total, 54 HD cycles in 4 different patients were recorded (Table 1). There were five HD cycles with incomplete data (twice due to patient non-compliance, twice due to equipment failure, in one dataset data on ultrafiltration were missing).

Electrical velocimetry

The EV monitor used in the study was an Aesculon® monitor supplied by Osypka Medical (Berlin, Germany). This commercially available monitoring device provides a continuous noninvasive cardiac output monitoring. By means of electrodes positioned on the neck and thorax, an alternating voltage is applied to the patient. The practical application of the device is comparable to ECG monitoring using four electrodes. The device records an electrocardiogram and measures thoracic bioimpedance. Bioimpedance, i.e., body tissue resistance to the applied electric alternating voltage, changes with respiration and cardiac cycle. Bioimpedance changes in relation to the ECG are used to calculate stroke volume and cardiac output. The EV algorithm [38] is based on the equation:

$$SV_{B-O} = \frac{V_{ITBV}}{\zeta^n} \sqrt{\frac{dZ/dt_{max}}{Z_0}} T_{LVE(c)}$$

where VITBV = intrathoracic blood; volume (ml); ζ = index of transthoracic, aberrant electrical conduction; dZ/dt_{max} = peak rate of change of the blood resistivity (velocity) component of the transthoracic cardiogenic impedance pulse variation (ohmic mean acceleration) (Ωs^{-2}); Z_0 = transthoracic base impedance (Ω); $\sqrt{(dZ/dt_{max})}/Z_0$ = acceleration step-down transformation (s^{-1}); and TLVE (c) = heart rate-corrected left ventricular ejection time(s) [38].

Table 1 Patient characteristics and hemodialysis (HD) cycles

Patient No	Predialytic weight mean ± SD [kg]	Fluid withdrawal mean ± SD [ml/kg]	No of HD cycles
1	16.6 ± 0.6	61.20 ± 12.12	4
2	42.2 ± 1.1	0 ± 0	19
3	38.1 ± 1.2	42.87 ± 17.74	20
4	36.7 ± 0.3	24.90 ± 11.22	11

Table 2 Cardiovascular parameters (mean) obtained by electrical velocimetry (EV) before/after hemodialysis (HD). Parameters analyzed were heart rate (HR), stroke volume (SV), stroke volume index (SI), cardiac output (CO), cardiac index (CI), thoracic fluid content (TFC), index of contractility (ICON), stroke volume variation (SVV), variation of ICON (VIC), R-R interval (TRR), pre-ejection period (PEP), left ventricular ejection time (LVET), systolic time ration (STR), and systemic vascular resistance index (SVRI). $N = 50$ HD cycles were included

Parameter	Before HD Mean	SEM	SD	After HD Mean	SEM	SD	Wilcoxon p
HR [1/min]	71.58	1.05	7.68	77.85	1.54	10.90	< 0.01
SV [ml]	85.09	2.57	18.89	70.71	2.08	14.73	< 0.01
SI [ml/m²]	65.61	1.32	9.68	60.42	1.32	9.69	< 0.01
CO [l/min]	6.02	0.17	1.26	5.39	0.13	0.91	< 0.01
CI [l/m²xmin]	4.67	0.09	0.67	4.14	0.07	0.52	< 0.01
TFC	40.54	0.44	3.23	36.15	0.49	3.43	< 0.01
ICON	104.60	2.61	19.15	95.51	2.25	15.94	< 0.01
SVV [%]	7.62	0.34	2.52	7.94	0.29	2.05	0.334
VIC [%]	11.90	0.73	5.38	12.95	0.51	3.61	0.037
TRR [ms]	847.73	11.78	86.60	785.10	14.64	103.51	< 0.01
PEP [ms]	101.36	1.00	7.35	109.49	2.03	14.37	< 0.01
LVET [ms]	308.12	2.25	16.52	284.07	2.65	18.71	< 0.01
STR	0.33	0.00	0.03	0.39	0.01	0.06	< 0.01
SVRI [dyn/m²]	1298.94	67.18	489.06	1610.61	51.31	362.84	0.242

The EV parameters provided by the device (Aesculon®) algorithm are heart rate (HR), stroke volume (SV), stroke volume index (SI), cardiac output (CO), cardiac index (CI), thoracic fluid index (TFC), index of contractility (ICON), stroke volume variation (SVV), variation of ICON (VIC), R-R interval (TRR), pre-ejection period (PEP), left ventricular ejection time (LVET), and systolic time ration (STR). Thus this continuous noninvasive monitoring device generates data on standard macro-hemodynamic parameters (HR, SV, SI, CO, CI, SVV), on parameters associated with the cardiac electric ECG cycle (TRR, STR), on parameters that can be used to assess contractility (ICON, VIC, LVET, PEP), and on fluid status (TFC). For a detailed description of the individual EV parameters, see [4].
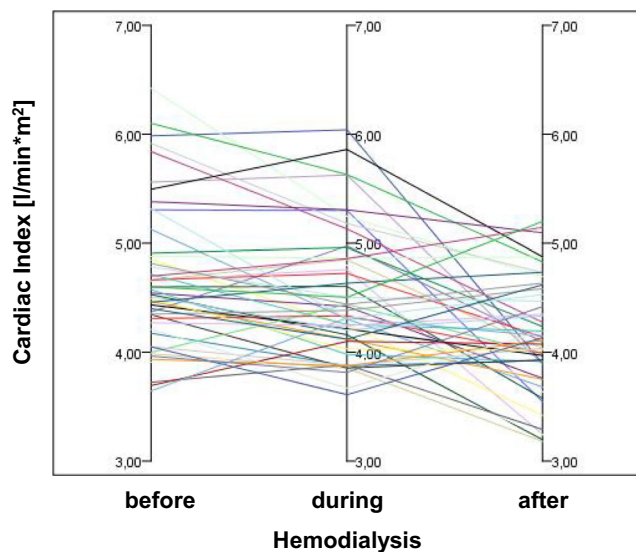
Study protocol

EV monitoring was recorded in supine patient position. Electrode position was chosen on the right lateral side of the neck and left lateral side of the trunk. Three sets of EV measurements for each measurement of the above cardiovascular parameters averaged over 30 s were obtained before HD, during HD, and immediately after HD. Systemic vascular resistance index (SVRI) was calculated before and after each HD cycle based on mean blood pressure and an assumed central venous pressure of 3 mmHg. Indexed values were related to body surface.
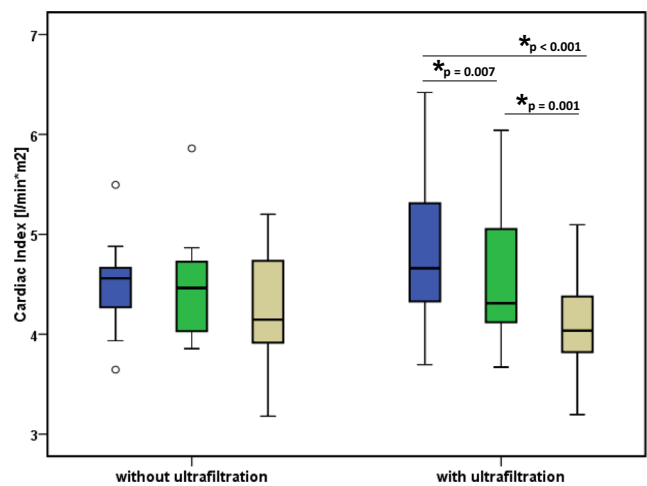

Fig. 1 Cardiac index: before hemodialysis (HD), during HD, and after HD. Each color-coded line represents an individual HD cycle ($n = 50$ HD cycles)

Fig. 2 Cardiac index (CI) without and with ultrafiltration: before (blue), during (green), and after (gray) hemodialysis (HD). Without ultrafiltration, there was no significant difference between the different points of time. With ultrafiltration, the difference was significant at each point in time (*, Wilcoxon rank test). The sample size was 18 HD cycles without ultrafiltration and 31 HD cycles with ultrafiltration. Box plots are presented with median, inter quartile range (IQR), 95% confidence intervals and outliers

Statistical analysis

Relative and percentage differences were calculated for the individual parameters. Spearman's correlation and significance (based on Wilcoxon rank test) were calculated. Linear mixed models were fitted to the differences in each EV parameter comparing measurements before and after HD. In initial models, patient was assumed a random effect, the individual HD cycles with patient as repeated measure and ultrafiltration per kg body weight as a fixed effect. The analyses were adjusted for the baseline value of the respective dependent variable by including it as a covariate in the model. In the final models, the random effect "patient" was omitted because it was not significant. Significance level was set at $\alpha = 5\%$.

Results

Mixed model analyses indicated that patient-specific variation regarding the various dependent variables was negligible. Influencing factors on the EV measurement differences before and after HD were ultrafiltration per kg body weight and height of initial EV measurements. Mixed model results revealed significant effects of ultrafiltration rate on the parameters HR ($p < 0.01$), SV ($p < 0.01$), SI ($p < 0.01$), CO ($p < 0.01$), TFC ($p < 0.01$), ICON ($p < 0.01$), SVV ($p = 0.03$), TRR ($p < 0.01$), PEP ($p < 0.01$), STR ($p < 0.01$), whereas its effects on CI ($p = 0.09$) and VIC ($p = 0.24$) were not significant.

Absolute values for individual cardiovascular EV parameters are summarized in Table 2. Each of the parameters was recorded at three time points – before, during, and immediately after HD. As an example, the recorded dataset structure combined CI measurements for the individual HD cycles are demonstrated in Figs. 1 and 2. Table 3 and Fig. 3 summarize HD effects on EV measurements as percentage difference between the initial recording before HD and the recording after HD. Effects on cardiovascular parameters were also seen in HD cycles without fluid withdrawal. The correlations between fluid withdrawal (ultrafiltration rate) and cardiovascular EV parameters are shown in Table 4.

Discussion

The study aim was to assess whether EV is capable of detecting an effect of HD on hemodynamic parameters in pediatric HD patients. The presented study data did show significant effects of HD on EV monitoring parameters. The effects of HD on EV were correlated to the amount of fluid withdrawal (ultrafiltration) during the individual HD cycles. In addition, in isovolemic HD cycles without fluid withdrawal significant effects were seen (see Table 3). Linear mixed model analysis did show that the amount of fluid withdrawal (ultrafiltration) was the main influencing factor. Most hemodynamic EV parameters did correlate with the amount of fluid withdrawal during HD. We would interpret the correlation data shown in Table 4 that the physiological effects of a reduced ventricular

Table 3 Relative difference [%] of parameters obtained by electrical velocimetry (EV) before /after hemodialysis (HD) with ultrafiltration ($n = 31$ HD cycles) and without ultrafiltration ($n = 18$ HD cycles). Parameters analyzed were heart rate (HR), stroke volume (SV), stroke volume index (SI), cardiac output (CO), cardiac index (CI), thoracic fluid content (TFC), index of contractility (ICON), stroke volume variation (SVV), variation of ICON (VIC), R-R interval (TRR), pre-ejection period (PEP), left ventricular ejection time (LVET), systolic time ration (STR), and systemic vascular resistance index (SVRI)

Parameter	Difference after HD [%]				Difference after HD without ultrafiltration [%]				Difference after HD with ultrafiltration [%]			
	Mean	SEM	SD	p	Mean	SEM	SD	p	Mean	SEM	SD	p
HR	8.9	1.4	10.1	<0.01	5.5	2.2	9.5	0.03	10.7	1.8	10.3	<0.01
SV	−17.5	1.5	10.5	<0.01	−9.8	1.5	6.6	<0.01	−22.2	1.7	9.7	<0.01
SI	−17.6	1.5	10.4	<0.01	−10.0	1.5	6.5	<0.01	−22.3	1.8	9.8	<0.01
CO	−10.3	1.9	13.2	<0.01	−4.6	2.8	12.1	0.13	−14.0	2.3	12.8	<0.01
CI	−10.3	1.9	13.2	<0.01	−4.5	2.8	12.0	0.13	−14.0	2.3	12.8	<0.01
TFC	−10.2	1.3	8.9	<0.01	−4.1	1.5	6.2	0.01	−13.3	1.5	8.3	<0.01
ICON	−7.2	2.0	14.1	<0.01	−4.8	2.1	9.0	0.04	−8.5	3.0	16.5	<0.01
SVV	19.1	8.0	56.2	0.02	−13.3	7.0	29.7	0.08	37.9	10.9	60.6	<0.01
VIC	33.3	11.6	82.3	<0.01	−3.9	6.1	26.1	0.53	56.0	17.3	96.4	<0.01
TRR	−7.4	1.2	8.7	<0.01	−4.6	2.1	8.9	0.04	−8.9	1.5	8.5	<0.01
PEP	7.9	1.9	13.3	<0.01	−4.8	1.2	5.1	<0.01	15.2	2.0	11.0	<0.01
LVET	−7.8	0.7	4.8	<0.01	−5.3	0.8	3.3	<0.01	−9.2	0.9	5.0	<0.01
STR	17.5	2.5	17.5	<0.01	0.4	1.7	7.4	0.82	27.3	2.5	13.8	<0.01
SVRI	−0.9	3.3	23.3	0.78	0.2	3.4	14.6	0.95	−1.8	5.1	27.8	0.73

filling were not fully compensated for by the cardiovascular response resulting in a reduced cardiac output despite increased heart rate after dialysis.

The observed findings were in concordance with methodical considerations on EV. The results were also consistent with data obtained by other monitoring methods on the effects of HD on circulation [26, 28–34].

Significant effects by HD were observed for all examined parameters except SVRI. This is in contrast to literature data on adults, where impedance cardiography monitoring was used in HD patients [34, 39, 40] and an effect on SVRI was observed. SVV as a hemodynamic monitoring parameter is usually applied in mechanically ventilated patients. Therefore, the parameter SVV is not adequate for the study setting of spontaneously breathing children. Nevertheless a significant effect of HD on SVV was seen for HD cycles with fluid withdrawal.

The basic impedance Z_0 (a parameter analogous to TFC) will change with body water content and with altered body osmolality. In a HD cycle, net fluid removal may lead to an increase in osmolality. In contrast, removal of urea and other small molecules may result in a marked decrease in blood osmolality [41]. Lower osmolality causes an increase in basic impedance Z_0, equivalent to a lower TFC, as observed in our series in patients with and without net ultrafiltration during HD. In contrast, an increase in hematocrit leads to a decrease in Z_0 [42]. Thus, HD effects on Z_0 (analogous to TFC) may be antagonistic regarding a possible osmolality reduction and a simultaneous increase of hematocrit. Nevertheless, a positive correlation between UF and TFC could be shown. The factors dZ/dtmax and TLVEC = LVET are affected by the cardiac cycle times PEP, LVET, and STR measured by the device. With decreased cardiac preload and filling during HD, calculated SV will theoretically fall. This has been shown in our data and is consistent with literature data [26, 28–33]. The theoretical effect of a decrease of Z_0 due to HD did not lead to increased SV measurements. HR did increase with HD – not fully compensating for lower SV – thus resulting in a decreased CI at the end of HD.

Presently available literature data on EV provide conflicting evidence regarding concordance with reference methods [9–19, 21, 22, 24–27]. Formal concordance studies comparing the noninvasive monitoring method EV to invasive "gold standard" methods such as the Fick principle in pediatric patients or subjects are difficult to ethically justify. Therefore data had to be derived from animal models [24, 25]. Nevertheless – despite the imprecisions of the methods involved – a positive correlation between EV reference methods may be assumed [27]. In our own pediatric data [19], the true precision of the method EV was 24.9% (based on three consecutive cardiac cycles as measuring interval). According to [35] the following theoretical considerations apply: The precision of a technique is considered to be two times the coefficient of variation (CV) or two times the coefficient of error
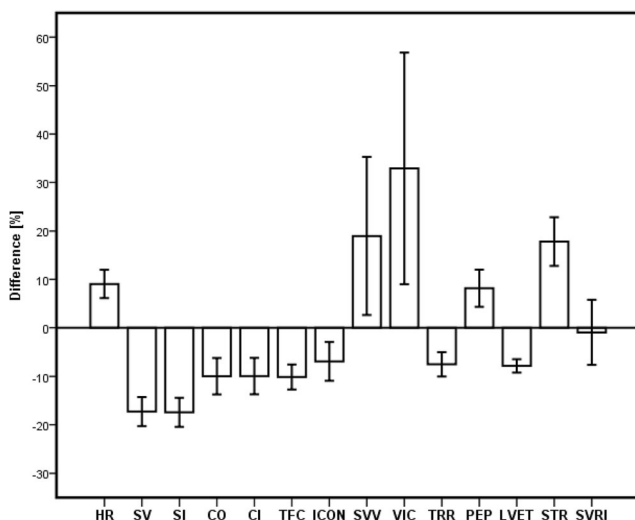

Fig. 3 Percentage difference of impedance cardiographic parameters comparing values before and after hemodialysis (HD, $n = 49$ cycles) based on the data shown in Table 3. Parameters analyzed were heart rate (HR), stroke volume (SV), stroke volume index (SI), cardiac output (CO), cardiac index (CI), thoracic fluid content (TFC), index of contractility (ICON), stroke volume variation (SVV), variation of ICON (VIC), R-R interval (TRR), pre-ejection period (PEP), left ventricular ejection time (LVET), systolic time ration (STR), and systemic vascular resistance index (SVRI). The differences for all parameters were significantly different from zero except for SVRI

Table 4 Spearman's correlation of percentage differences of parameters obtained by electrical velocimetry (EV) before/after hemodialysis (HD) with ultrafiltration/kg body weight ($n = 49$ HD cycles). Parameters analyzed were heart rate (HR), stroke volume (SV), stroke volume index (SI), cardiac output (CO), cardiac index (CI), thoracic fluid content (TFC), index of contractility (ICON), stroke volume variation (SVV), variation of ICON (VIC), R-R interval (TRR), pre-ejection period (PEP), left ventricular ejection time (LVET), systolic time ration (STR), and systemic vascular resistance index (SVRI). Spearman's correlation was significant for all parameters except ICON and SVRI

Parameter	Correlation (Spearman's rho)
HR	0.31
SV	−0.63
SI	−0.63
CO	−0.32
CI	−0.32
TFC	−0.62
ICON	−0.09 (n.s.)
SVV	0.46
VIC	0.34
TRR	−0.30
PEP	0.76
LVET	−0.53
STR	0.81
SVRI	−0.07 (n.s)

(CE). When one only measurement method is used, CE is equal to CV. The least significant change (LSC) is the minimum change that needs to be measured by a monitoring device in order to recognize a real change. It is LSC = precision √2, with precision = 2 CV. By choosing a longer measurement sample of two sets of 30 s measurement cycles at each measurement point in this study, CE in the setting of this study was based on an average of 71 cardiac cycles rather than on 3 cardiac cycles [19] as in our previous study. According to [35], the estimated coefficient of error (CE) based on the coefficient of variation (CV) for the individual measurement is CE = CV / √n. These theoretical considerations [19, 35] on the EV parameter SV result in a CV of 5.1% and LSC of 7.2% in the setting of our study. The SV changes in association to HD observed in the study were 17% and thus above the theoretical LSC.

In our opinion, the advantages of noninvasiveness and continuity of EV outweighs the disadvantage of imprecision and partial lack of formal assessment in comparison to (invasive) reference methods. The monitoring tool EV could be helpful in (pediatric) dialysis patients regarding several aspects:

- TFC could be used as an additional parameter to assess the patient's fluid status. Bioimpedance (which is comparable to the EV parameter TFC) has been studied with other devices in the setting of hemodialysis [5–7, 39, 40, 43, 44].
- The cardiovascular parameters CI and SVRI could be used to monitor and interpret circulation in potentially low cardiac output situations. The monitoring parameters could distinguish between reduced cardiac output and inadequate systemic vascular resistance. In adults, studies on cardiovascular parameters have been published [30–34, 39, 40]. A study with a different impedance cardiography device did observe similar changes in children during HD as we did [44]. The results are consistent with a previous study on impedance cardiography [26], which showed stroke volume changes in adults during HD correlated to echocardiographic measurements.
- The additional hemodynamic EV cardiac parameters such as ICON, TRR, PEP, LVET, and STR could be used to monitor cardiac function particularly in children with, e.g., renal hypertension and secondary cardiac impairment.

The study aim was to assess whether EV is able to detect changes of hemodynamic parameters during pediatric HD. The obtained data were purely observational. No correlation to echocardiographic findings or laboratory parameters is provided. Assessment of the prognostic or therapeutic relevance of the measured data is subject to future research.

EV or impedance cardiography provides additional hemodynamic information compared to "bioimpedance" as assessment of fluid status alone. Thus, goal-directed dialysis management based on EV or impedance cardiography parameters might improve prognosis and outcome of (pediatric) HD patients. Cardiovascular EV parameters might be included in elaborate HD algorithms. Prognostic relevance of these data might be assessed by the use of registries [45] on pediatric HD patients. As artificial intelligence and learning systems appear on the horizon [46, 47], it seems logical to use the information contained in the circulatory EV parameters for control of dialysis. Of course, algorithms then would have to be tested with suitable endpoints tailored for pediatric HD patients.

There are several limitations of the study. There was no confirmation of the EV measurements by an alternative monitoring method. We can state a variation in measurement, of which one may assume that it represents a true change in hemodynamic parameters. But in this particular setting without a reference method, the "true" hemodynamic parameters remain uncertain. This weakens the conclusion of the study. However, literature data [27] including our own data [19] on stroke volume measurement by EV shows correlation to reference methods depending on the individual patient groups. An adult study comparing stroke volume changes during HD showed a good correlation between impedance cardiography and echocardiography [26]. The EV parameter changes observed during HD were consistent with the physiological considerations as presented in the discussion on the effect of dialysis on circulatory parameters. Reference methods to obtain the other parameters specifically generated by the Aesculon® EV device are not easily available for pediatric patients. Therefore, and for compliance reasons of the pediatric patients, we have abstained from the inclusion of a reference measurement in the study. Theoretical data on precision of EV in detecting parameters other than SV (and the deduced parameters CO and CI) are not available – therefore the small observed changes in several other EV parameters might be below the level required to detect a real change. The study sample is small. HD in children is a rare event. This study does not take laboratory data on uremic clearance during HD into account. Therefore, no correlation between TFC and uremia can be provided.

In conclusion, pediatric HD did change hemodynamic EV monitoring parameters. EV parameters did change after HD with fluid withdrawal and to a lesser extent also after isovolemic HD. Therefore, EV may be a tool to monitor cardiovascular effects during pediatric HD beyond mere volume changes caused by fluid withdrawal.

interpretation. HOP developed the linear mixed model analysis. All authors approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local ethical board ("Ethikkommission der Ärztekammer Hamburg"). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed parental consent was obtained from all individual participants included in the study.

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