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# Assessment of pleth variability index in volume changes during ultrafiltration process

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## Abstract:

**OBJECTIVES:** Pleth variability index (PVI) has been studied mostly in mechanically ventilated patients, and the role of PVI in predicting volume status and volume changes among spontaneously breathing patients is not clear in the literature. We hypothesized that hemodialysis (HD) can be a valid model for a simulation that can be evaluated the correlation of PVI with fluid changes in various volume states. The aim of this study was to investigate the utility of PVI for assessing volume changes in HD patients who are breathing spontaneously.

**METHODS:** This prospective, observational study included patients aged 18 years or older who had end-stage renal failure and presented for routine HD between December 2019 and January 2020. PVI values were measured before and after HD session. Changes in PVI levels were compared according to the amount of ultrafiltration.

**RESULTS:** A total of sixty patients were included. Mean PVI level before HD ( $20.7\% \pm 5\%$ ) showed a statistically significant increase to  $27.7\% \pm 6\%$  after HD session ( $P < 0.001$ ). According to the amount of fluid removed during HD, the changes in PVI were statistically significant ( $P = 0.015$ ). There was a strong correlation between  $\Delta$ PVI and ultrafiltrated volume ( $r = 0.744$ ,  $P < 0.001$ ).

**CONCLUSION:** The fluid removed by HD caused increase in PVI, and the increase was strongly correlated with the amount of volume change. Bedside monitoring of PVI may provide the clinicians with useful information for monitoring the volume status in critically ill patients with spontaneous breathing.

## Keywords:

Hypervolemia, hypovolemia, pleth variability index, ultrafiltration, volume status

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## Introduction

Both hypovolemia and hypervolemia are known to negatively affect the prognosis of critically ill patients.<sup>[1-3]</sup> However, other pathological conditions that may be added to an existing pathology in the absence of knowledge of the basal-volume status may expose clinicians with complex hemodynamic presentations. In such circumstances, clinicians may be guided by effective measurement techniques of

both assessing volume status and guiding fluid-resuscitation therapy.

Many volume-assessment methods have been reported in the literature. Dynamic measurements (stroke-volume variation, aortic-flow measurement, etc.), which are believed to yield the most accurate results, have limited use in daily practice due to the requirement for invasive interventions.<sup>[4,5]</sup> On the other hand, the data on the effectiveness of ultrasonographic measurements (inferior vena cava collapsibility index, carotid flow time measurement, etc.), the most

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**Box-ED Section:****What is already known on the study topic?**

- As both hypovolemia and hypervolemia have a negative impact on prognosis, the first step in fluid-resuscitation therapy in critically ill patients is the accurate assessment of the volume status
- Pleth variability index (PVI) is a bedside, rapid, reproducible, and user-independent noninvasive parameter and has been reported to be associated with volume status.

**What is the conflict on the issue?**

- PVI, measured during a complete respiratory cycle, has been studied mostly in mechanically ventilated patients
- Since a standard tidal volume cannot be attained by each spontaneous breath, PVI has been claimed to have questionable accuracy and reliability during spontaneous ventilation.

**How is this study structured?**

- This was a single-center, prospective observational study includes data from sixty patients aged 18 years or older who had end-stage renal failure and received routine hemodialysis (HD) session.

**What does this study tell us?**

- Mean PVI level before HD showed a statistically significant increase after HD session. According to the amount of fluid removed during HD, the changes in PVI were also statistically significant, and there was a strong correlation between  $\Delta$ PVI and ultrafiltrated volume
- Unlike previous studies, there was a significant volume change in this study. Although PVI is known to be less sensitive to minimal volume changes, the present study may indicate that PVI may effectively reflect volume status in cases of marked volume changes in patients with regular and normal spontaneous breathing.

intensively studied techniques so far, are conflicting due to operator- and patient-dependent factors.<sup>[6-9]</sup> Recently introduced in the literature, the pleth variability index (PVI) has drawn increased attention as a bedside, rapid, reproducible, and user-independent parameter that is free of the limitations of other measurement techniques. However, PVI has been studied mostly in mechanically ventilated patients, and in spite of its great potential during triage, pre-evaluation, and clinical follow-up, only a limited number of studies have addressed the role of PVI in predicting volume status and volume changes among spontaneously breathing patients.<sup>[3,4,10,11]</sup>

Hemodialysis (HD) is a procedure that includes fluid removal (ultrafiltration [UF]) simultaneously with the removal of waste solutes.<sup>[12]</sup> Although it is not possible to determine exactly a patient's volume load or deficit in clinical practice, the amount of volume removed during HD can be precisely known. Therefore, we hypothesized that HD can be a valid model for a simulation that can be evaluated the correlation of PVI with volume changes in various volume states. The aim of this study was to investigate the utility of PVI for assessing volume changes in HD patients who are breathing spontaneously.

## Subjects and Methods

### Study design and setting

This prospective, observational study was conducted between December 2019 and January 2020 at a private dialysis center approved by the Turkish Ministry of Health. The local ethics committee approved the study (Kecioren Training and Research Hospital Ethics Committee; Date: November 13, 2019; No: 2012-KAEK-15/1995), and all patients provided written, informed consent before PVI measurement.

### Study population

This study included patients aged 18 years or older who had end-stage renal failure and presented for routine HD therapy at the dialysis center at which the study was performed. The exclusion criteria were as follows: attending a routine HD program for <3 months; having active infection, peripheral vascular disease, systolic blood pressure (SBP) below 90 mmHg before or during HD, or a volume of fluid removal <1000 cc in HD; being unable to complete HD; being pregnant; problems that prevented PVI from being measured with a pulse oximeter for any reason; and having nails painted with nail polish or henna, which reduces the reliability of PVI measurement.

### Study protocol

Before the HD session, all the patients were evaluated in line with their height, weight, body surface area (calculated from these data), and dry weights by a team of nephrologist, the doctor, and the nurse, who followed up during the procedure at the HD center where the study was conducted. As a result of this evaluation, the appropriate dialysate and the device membrane were selected for each patient, and in addition, the amounts of fluid to be withdrawn from the patients were calculated with the standard method in line with these data. The patients' PVI levels were first measured before the onset of the HD session using an extremity that was free of active arteriovenous fistula or an HD catheter. PVI was measured at room temperature by putting a pulse oximeter sensor connected to a Massimo Root device on a patient's second, third, or fourth finger while

the patient’s hand was held at heart level. The device automatically calculated the PVI as a percentage (%) using the infrared absorption spectroscopy technique. All measurements were recorded when a stable value was obtained on the device after waiting at least 3 min. The PVI measurements were repeated immediately after completion of the HD sessions. In addition, demographic data, comorbidities, body weight, and vital signs were measured before and after the HD session, and the volume of fluid removed during HD was recorded. The patients were divided into three groups according to the amount of fluid removed in HD.

**Statistical analysis**

The study’s data were statistically analyzed using IBM SPSS 24.0 (Chicago, IL, USA). The normality of the distribution of numeric variables was tested using the Shapiro–Wilk test. Numeric variables were presented as mean ± standard deviation (SD) or median (25%–75% quartiles), and categorical variables were presented as the number of cases and percentage (%). The dependent numeric variables were analyzed using a paired sample *t*-test, and the nonparametric variables were tested using a Wilcoxon test. According to the amount of fluid removed during dialysis, an ANOVA or a Kruskal–Wallis test was used to compare the changes in the parametric and nonparametric data, respectively. The correlation between the volume of fluid removed during dialysis and the change in PVI was analyzed using a Pearson’s correlation test, and the correlation between the volume removed and the change in vital signs was analyzed using a Spearman’s correlation test. Statistical significance was accepted as *P* < 0.05.

**Sample size calculation**

The sample size was estimated using G\*Power for Mac OS X (version 3.1.9.2, Universitat Düsseldorf, Germany). A 2% change in PVI between measurements was considered clinically significant. In addition, an SD level of 4% was considered, as indicated by a previous study.<sup>[3]</sup> Therefore, assuming a two-sided alpha 0.05, a sample size of sixty patients was anticipated to achieve 95% power.

**Results**

This study included sixty HD patients, of whom 29 (48.3%) were male, and their mean age was 66.2 ± 10.8 years. The median volume of fluid removed during HD was 3500 mL (interquartile range [IQR] 25%–75%: 2500–4000 mL). Table 1 shows the patients’ demographic data and the median amount of UF.

A comparison of vital signs, body weight, and PVI levels before and after the HD session showed a significant reduction in mean arterial pressure (MAP) and body weight after the HD session (*P* < 0.001 for both). In

contrast, the mean PVI level, which was 20.7% ± 5% before the HD session, showed a statistically significant increase to 27.7% ± 6% (*P* < 0.001) [Table 2]. Figure 1 shows PVI level changes in all patients during HD.

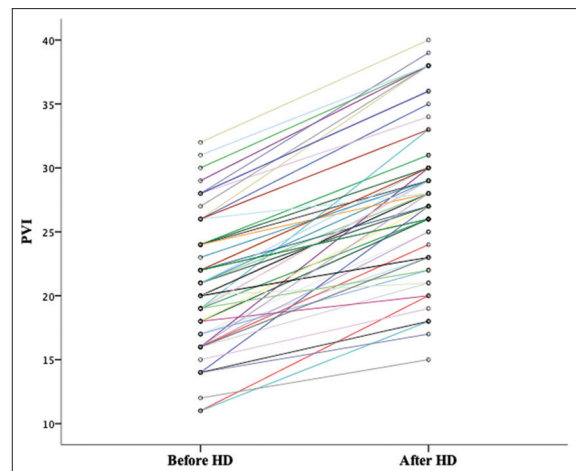
Whereas PVI increased by only 3% ± 1.1% in those patients from whom <2000 mL of fluid was removed during HD, PVI increased by 9.8% ± 2.5% in those from whom ≥4000 mL of fluid was removed. Table 3 shows the PVI levels before and after the HD session and the changes in PVI according to the amount of fluid removed. When the changes in vital signs and PVI levels were compared according to the amount of fluid removed during HD, the changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, and PVI were statistically significant [Table 4].

There was a statistically significant but weak-to-moderate correlation between the amount of fluid removed during HD and the change in SBP (*r* = 0.429, *P* = 0.001), DBP (*r* = 0.406, *P* = 0.001), and MAP (*r* = 0.461, *P* < 0.001). In contrast, there was a strong correlation between ΔPVI and ultrafiltrated volume (*r* = 0.744, *P* < 0.001) [Table 5 and Figure 2].

**Table 1: Demographic data of hemodialysis patients and amount of fluid removed by hemodialysis**

	<i>n</i> (%)
Gender	
Male	29 (48.3)
Age (mean±SD)	66.2±10.8
BMI (kg/m <sup>2</sup> ), median (IQR 25-75)	25.1 (22.8-27.8)
Comorbidity	
Hypertension	57 (95)
Coronary artery disease	41 (68.3)
Diabetes mellitus	20 (33.3)
Chronic heart failure	16 (26.7)
Fluid removed (mL), median (IQR 25-75)	3500 (2500-4000)

BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range



**Figure 1: Pleth variability index level changes in all patients during hemodialysis**

**Table 2: Comparison of vital signs, body weight, and perfusion variability index values before and after hemodialysis**

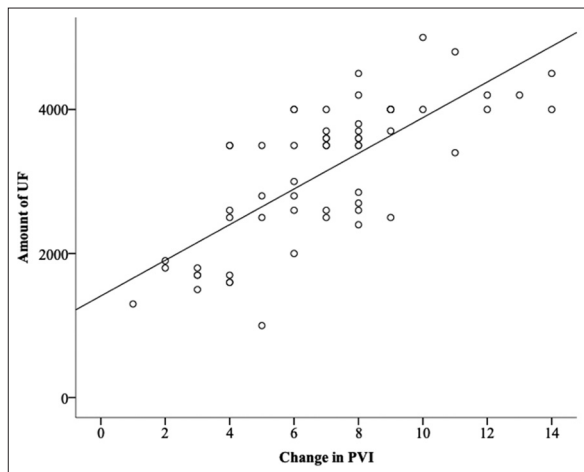
	Before HD	After HD	P
SBP, median (IQR 25-75)	130 (120-143.7)	120 (110-120)	<0.001
DBP, median (IQR 25-75)	80 (70-88.5)	70 (60-78.7)	<0.001
MAP, median (IQR 25-75)	96.6 (87.5-105.8)	86.6 (76.6-93.3)	<0.001
HR, median (IQR 25-75)	70 (66-78)	72 (66-79.5)	0.353
RR, median (IQR 25-75)	18 (17-19)	18 (16.2-18.7)	0.387
Body weight (mean±SD)	72.4±12.4	69.6±12.3	<0.001
PVI (mean±SD)	20.7±5	27.7±6	<0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, HR: Heart rate, RR: Respiratory rate, PVI: Perfusion variability index, HD: Hemodialysis, SD: Standard deviation, IQR: Interquartile range

**Table 3: The perfusion variability index values before and after hemodialysis and changes in perfusion variability index according to amount of ultrafiltration**

Fluid removed (mL)	Mean±SD		
	PVI before HD	PVI after HD	Change in PVI
Group 1 (UF <2000)	18.5±4.5	21.5±4.5	3±1.1
Group 2 (UF 2000-3999)	21.4±4.9	28.3±5.5	6.8±1.6
Group 3 (UF ≥4000)	20.9±5.5	30.8±5	9.8±2.5

PVI: Perfusion variability index, HD: Hemodialysis, UF: Ultrafiltration, SD: Standard deviation



**Figure 2:** Correlation between the amount of fluid removed and changes in pleth variability index

## Discussion

In the present study, which investigated the utility of measuring PVI to assess volume changes, we reached two important results. First, we detected a statistically significant increase in PVI levels at the post-HD phase, after fluid removal, compared to PVI levels measured at the pre-HD phase. This result supports the idea that PVI measurement can also be used to differentiate various volume status among not only mechanically ventilated patients but also spontaneously breathing ones. Second, we found that the increase in PVI changed according to the volume removed during HD and that this change was statistically significant. In our study, ΔPVI had a

strong correlation with the amount of fluid removed. Based on the above data, we believe that monitoring PVI, a noninvasive, bedside, rapid, and reproducible parameter, may provide clinicians with valuable data for monitoring treatment and assessment its efficacy among patients requiring volume restoration.

Because both insufficient and excessive volume restoration increase mortality, determining and monitoring volume status have become increasingly important for managing critically ill patients. Multiple studies have reported various limitations of both invasive and noninvasive methods and the inconsistent data about them, raising questions about their feasibility in daily practice.<sup>[13]</sup> In contrast, PVI has recently been reported to be a good predictor of volume status and treatment response among mechanically ventilated patients.<sup>[14,15]</sup> However, the data on PVI in spontaneously breathing patients are quite limited. Keller *et al.* reported a mean PVI of 18.3% ± 9.4% in spontaneously breathing, healthy volunteers during the passive leg raising (PLR) maneuver, which increases cardiac output, and PVI increased to 25.4% ± 10.6% after the patients were placed in a semi-recumbent position.<sup>[4]</sup> In a heterogeneous study population of 44 subjects that included 20 patients undergoing UF and 24 blood donors, Schoonjans *et al.* reported a mean PVI of 18% ± 7% before the procedures and a mean PVI of 22% ± 10% after the UF or blood donation.<sup>[10]</sup> In the present study, we found that the pre-HD mean PVI (20.7% ± 5%) increased significantly in the post-HD phase (27.7% ± 6%), after fluid removal. A significant change in the PVI levels between the baseline relative hypervolemia phase and the HD-induced relative hypovolemia phase supports the idea that PVI can also be used to assess various volume status in patients who are breathing spontaneously.

When monitoring treatment response in critically ill patients, there is an ongoing need for novel parameters that consistently correlate with volume status changes. Traditional noninvasive parameters, including vital signs and urine output, cannot provide adequate information in a real-time, rapid, effective manner in daily practice.<sup>[14]</sup> Emektar *et al.* reported no significant change in PVI



**Table 4: Comparison of changes in perfusion variability index and vital signs in patient groups with different amounts of fluid removed**

	Group 1 (UF <2000 mL) (n=11)	Group 2 (UF 2000-3999 mL) (n=32)	Group 3 (UF ≥4000 mL) (n=17)	P
ΔPVI (mean±SD)	3±1.1	6.8±1.6	9.8±2.5	0.015*
ΔSBP, median (IQR 25-75)	10 (5-10)	10 (10-20)	20 (15-30)	0.005#
ΔDBP, median (IQR 25-75)	10 (0-10)	10 (0-10)	20 (10-40)	<0.001#
ΔMAP, median (IQR 25-75)	10 (3.3-11.7)	10 (3.3-13.3)	20 (10-36.7)	0.002#
ΔHR, median (IQR 25-75)	0 (-3-2)	0 (-2-2)	0 (0-4)	0.357#
ΔRR, median (IQR 25-75)	0 (-1-1)	0 (-1-1)	-1 (-2-1)	0.759#

\*Statistically significant differences were found between all patient groups in terms of ΔPVI values in *post hoc* tests, #After Bonferroni correction, a new P value was accepted as 0.016. PVI: Perfusion variability index, UF: Ultrafiltration, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, HR: Heart rate, RR: Respiratory rate, SD: Standard deviation, IQR: Interquartile range

**Table 5: Correlation between the amount of fluid removed and changes in perfusion variability index and vital signs**

	Correlation coefficient	P
ΔPVI, mean±SD	0.744	<0.001
ΔSBP, median (IQR 25-75)	0.429	0.001
ΔDBP, median (IQR 25-75)	0.406	0.001
ΔMAP, median (IQR 25-75)	0.461	<0.001
ΔHR, median (IQR 25-75)	0.210	0.107
ΔRR, median (IQR 25-75)	-0.066	0.618

PVI: Perfusion variability index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, HR: Heart rate, RR: Respiratory rate, SD: Standard deviation, IQR: Interquartile range

after rehydrating mildly dehydrated patients who had acute gastroenteritis, whereas they showed a significant PVI (5%) reduction as a result of fluid replacement in a moderately/severely dehydrated group, which had greater fluid deficits. Based on these results, the authors suggested that the accuracy and reliability of PVI levels for reflecting volume status increased as the change of fluid amount increased.<sup>[11]</sup> In accordance with this view, the present study detected a greater PVI change as the volume of the fluid removed increased. Furthermore, whereas the present study showed a weak-to-moderate correlation between the change in fluid status and the change in blood pressure, one of the most commonly used noninvasive static parameters, change in fluid status, showed a strong correlation with ΔPVI ( $r = 0.744$ ,  $P < 0.001$ ). We believe that such a strong correlation supports the utility of PVI for monitoring treatment response during volume removal among patients who have volume overload in clinical practice.

In the literature, the biggest gap in evidence regarding PVI is its questionable accuracy and reliability during spontaneous ventilation. Because PVI, measured during a complete respiratory cycle, is a dynamic indicator that relies on cardiopulmonary interactions, more consistent measurements have been reported during mechanical ventilation.<sup>[16,17]</sup> It has been argued that the reliability of PVI measurement is reduced during spontaneous ventilation because a standard tidal volume cannot be attained by each spontaneous

breath.<sup>[18]</sup> Besides, PVI is known as a parameter indirectly related to the pulsus paradoxus, and it has also been suggested that tachypnea may affect the measurement.<sup>[19]</sup> Furthermore, it has been reported in the literature that hypercapnia causes a decrease in PVI, so respiratory rate is considered to be important in the accuracy of PVI measurement.<sup>[20]</sup> Conflicting data on PVI measurements during spontaneous breathing have been attributed to all these factors.<sup>[21]</sup> However, a majority of these studies, which had relatively small study populations with normal respiratory states, used the PLR maneuver, which causes a sudden increase in preload, to assess volume change and fluid unresponsiveness.<sup>[3,4,10,21]</sup> On the other hand, in clinical practice, gradual and controlled treatment protocols are used in volume removal or fluid replacement, rather than sudden restorations in critically ill patients. In our study, which all patients also have normal respiratory rates, a gradual removal of volume during HD that was similar to that in daily practice may have caused an increase in PVI that was consistent with the amount of volume change. In addition, the amount of change in preload induced by PLR is about 250–300 mL.<sup>[22]</sup> However, in the present study, the median volume change was 3500 mL. The consistent significance and strong correlation detected in the present study may indicate that PVI is not sensitive to minimal volume changes; however, it may effectively reflect volume status in cases of marked volume changes, regardless of the ventilation mode. Based on the results of the present study, we believe that PVI may also be used to monitor volume status in spontaneously breathing patients who have severe volume overload. Although the study cohort did not include hypovolemic patients at baseline, the strong correlation with volume change suggests that PVI can be studied among spontaneously breathing patients with severe volume deficits in new clinical studies. Future randomized controlled trials in real-time clinical settings can clarify the clinical significance of this study's results.

### Limitations

The main limitation of our study is the lack of a clear distinction between patients' hypervolemic, euvoletic,

and hypovolemic volume status. In pre-HD status, the median fluid overload was 3500 mL (IQR 25%–75%: 2500–4000 mL), compared to post-HD status. While pre-HD status can be considered hypervolemic according to the dry body weights of patients who have chronic renal failure, it is possible that some patients may become euvolemic, some hypovolemic, and some even remain hypervolemic after HD. In addition, our study involved adult patients, and thus its results cannot be generalized to the pediatric population.

## Conclusion

In the present study, we found that the fluid removed by HD in spontaneously breathing patients caused an increase in PVI and that this increase was strongly correlated with the amount of volume change. Bedside monitoring of PVI, which is a noninvasive, fast, reproducible measurement parameter, may provide the clinicians with useful information for monitoring the volume status and evaluating the effectiveness of volume-restoration therapy in critically ill patients with spontaneous breathing.

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### Author contribution statement

Conception: S.D.; Design and supervision: S.D., H.U.; Data collection and processing: S.D., H.U.; Analysis and interpretation: S.D., H.U.; Literature review: S.D., H.U.; Writer: S.D., H.U.; Critical review: S.D., H.U.

### Conflicts of interest

None Declared.

### Ethical approval

Ethical approval for the present study was obtained from Kecioren Training and Research Hospital Ethics Committee (Date: November 13, 2019; No: 2012-KAEK-15/1995).

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