

Comparison of bedside assessed arm and leg fluid filtration determined by venous congestion plethysmography in perioperative cancer patients

An observational study investigating agreement

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Abstract

In recent years, pathophysiology and clinical impact of microvascular fluid filtration has regained interest. As the latest data in surgical patients have been published almost 20 years ago, there is need for further research to better understand fluid filtration during the perioperative period. Venous congestion plethysmography (VCP) provides a rapid and noninvasive method, which has been shown suitable for the assessment of fluid filtration in limbs. Fluid filtration assessed by VCP can be obtained from forearm and calf measurement sites, while in many clinical situations a reduced access to the patient often restricts the measurements to patient's forearm. We aimed to investigate if fluid filtration obtained from forearm and calf measurement site is interchangeable in nonsedated perioperative patients.

Fluid filtration by VCP was obtained simultaneously from forearm and calf in patients with ovarian cancer at 4 time points during the perioperative course and assessed by the difference of volume changes of the limb between third and sixth minutes (VC_{6-3min}) during venous congestion. VC_{6-3min} obtained from forearm and calf measurement sites was compared with respect to agreement and evaluated regarding the association with the presence of leg edema.

A total of 74 paired measurements were analyzed in 29 patients. Forearm VC_{6-3min} was significantly higher than calf VC_{6-3min} (median [25th; 75th quartile], 0.6 (0.4; 0.9) vs 0.4 [0.3; 0.6] %, $P=0.008$). Bland-Altman and Polar analysis revealed a poor agreement between forearm and calf VC_{6-3min} at predefined time points and changes of VC_{6-3min} during the perioperative course (bias +0.23%, limits of agreement [LOA] -1.1% to 1.6% ; angular bias -2.5° , radial LOA -82° to $+77^\circ$). Forearm VC_{6-3min} was significantly increased in patients with presence of leg edema (0.7 (0.5; 1.0) vs 0.5 (0.4; 0.6) %, $P<0.001$) while calf VC_{6-3min} did not differ in patients with and without edema.

Editor: Wilhelm Mistiaen.

This article was presented in part at the European Society of Anaesthesiology EUROANAESTHESIA 2015 Annual Meeting in Berlin, May 2015.

Study concept, design of the study: AF, CS.

Biometrical planning: AF.

Acquisition of data: AF, SH, J-JD.

Interpretation of data: OH, SH, CS, AF.

Statistical analysis: AK, OH, AF.

Drafting of the manuscript: OH, AF.

Critical revision of the manuscript for important intellectual content: all authors.

Final revision of manuscript: OH, AF.

Obtained funding: CS.

Study supervision: AF, CS.

This research was an investigator-initiated study that was funded by departmental sources. It was supported by ELCAT GmbH (Wolfratshausen, Germany) providing the mercury in-Silastic strain-gauge venous congestion plethysmography device within a loan agreement. The company had no input into, or control over, study design, data collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Ethical approval was given by the Ethical Committee of Charité—University Medicine Berlin (No. EA1/004/11).

The study was internationally subscribed: NCT01311297 (registered 08/03/2011, <https://clinicaltrials.gov/>).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:9(e6066)

Received: 19 November 2016 / Received in final form: 12 January 2017 / Accepted: 13 January 2017

<http://dx.doi.org/10.1097/MD.00000000000006066>

This study indicates that forearm and calf measurement sites are not interchangeable when bedside assessing fluid filtration by VCP in nonsedated perioperative patients. Considering that only forearm fluid filtration was related to the presence of edema, forearm measurement site should be chosen as a primary site for assessing fluid filtration.

Abbreviations: τ = time constant, ASA = American Society of Anesthesiology, CI = confidence interval, FIGO = Fédération Internationale de Gynécologie et d'Obstétrique, LOA = limits of agreement, OR = odds ratio, PE = percentage error, POD = postoperative day, RLOA = radial limits of agreement, RVR = rapid volume response, VC = volume changes, VCP = venous congestion plethysmography.

Keywords: agreement, edema, fluid filtration, perioperative, venous congestion plethysmography

1. Introduction

Microvascular fluid filtration is supposed a substantial issue in critical ill patients and patients undergoing major surgery,^[1,2] whereas the latest data in surgical patients have been published almost 20 years ago.^[3] In this regard, there is need for further research to better understand fluid filtration during the perioperative period.

In recent years, the traditional Starling principle has been modified in light of new insights into the role of the endothelial glycocalyx and endothelial surface layer, the role of endothelial extracellular matrix, and the role of lymphatic flow.^[2,4] Increased fluid filtration leading to interstitial edema formation can primarily result from abnormal Starling forces, alterations in endothelial permeability, or impaired lymphatic drainage.^[4] While the assessment of the revised Starling forces, such as difference in transendothelial pressure and difference in colloid osmotic pressure between plasma and the subglycocalyx space, is still reserved for experimental conditions, alterations in endothelial permeability can be assessed at bedside in the clinical setting.

In this regard, venous congestion plethysmography (VCP) provides a rapid and noninvasive method, which has been shown suitable for the clinical assessment of endothelial permeability in limbs.^[5] Fluid filtration assessed by VCP relies on changes in tissue volume of the limb in response to an increase in venous pressure. After the start of venous congestion an initial exponential change in limb volume is followed by a linear increase due to the alteration in interstitial volume secondary to fluid filtration.^[5]

Using VCP at bedside, alterations in fluid filtration have been shown in patients with diabetes,^[6] thrombosis,^[7] sepsis,^[8,9] and patients undergoing major vascular surgery^[3] while measurement sites varied among studies. Fluid filtration assessed by VCP can be obtained from forearm and calf measurement sites, while in many clinical situations there is reduced access to the patient often restricting the measurement site to patient's forearm.

Previous data regarding the interchangeability of forearm and calf measurement site are inconsistent with studies showing similar values of fluid filtration in forearm and calf,^[5] whereas other studies indicated a higher forearm fluid filtration than in the calf.^[10,11] However, these studies lacked the appropriate statistical methods to adequately assess agreement of fluid filtration between forearm and calf measurement site. In this regard, it remains uncertain if measurement sites of fluid filtration obtained by VCP at bedside are interchangeable in perioperative patients.

In this context, we aimed to investigate the agreement of fluid filtration between forearm and calf measurement sites in nonsedated patients during the perioperative course; and to evaluate the association of fluid filtration assessed by VCP from forearm and calf measurement site with the presence of peripheral edema.

2. Methods

This study is a prospective observational study comparing forearm and calf fluid filtration during the perioperative period in patients with epithelial ovarian cancer. The study was approved by the Ethical Committee of Charité—University Medicine Berlin (No. EA1/004/11) and the study was internationally subscribed (NCT01311297). The trial was conducted at Charité—University Medicine Berlin, Campus Virchow Klinikum, Berlin, Germany.

2.1. Subjects

Thirty female patients with epithelial ovarian cancer, aged 18 or older, who were admitted to the Department of Gynecology (European Competence Center for Ovarian Cancer, Charité—University Medicine Berlin, Campus Virchow-Klinikum) and who were scheduled for cytoreductive surgery participated in this study. Written informed consent was obtained from all patients prior to participating in the study.

2.2. Experimental setting

Fluid filtration was assessed by mercury in-Silastic strain-gauge VCP (Vasolab 5000, ELCAT GmbH, Wolfratshausen, Germany) at 4 predefined time points during the perioperative course (preoperative day, postoperative day 1 (POD1), POD3, and POD5). Patients were studied in a temperature-controlled room (21°–22°C) on the ward. Prior to experimental study visits, all patients refrained from physical activity for at least 30 minutes and were asked to remain still during measurements. After pulling off close-fitting clothes, patients were positioned supine and pneumatic cuffs with multiple air inlets to permit rapid inflation were applied to the right upper arm and the right thigh, approximately 3 to 5 cm proximal to the cubital and knee joint. A strain gauge sensor junction head was attached to the forearm and calf at the largest circumference using double stick discs. Hereafter, strain gauge sensors of the appropriate length were applied ensuring a tight-fitting placement on the skin and a minimum pretension. The leg was elevated while the heel was supported on a custom-built cushion resulting in knee and hip angles at 90° and a calf position approximately 20 cm above the heart level. The arm was abducted 45° and elevated 45° from supine position applying pads distal from the strain gauge mount ensuring a free positioning of the strain gauge sensor. The height above heart level was the same for the 2 measurement sites.

2.3. Experimental protocol

All measurements were performed by the members of the study group well trained in handling with VCP. Measurements were performed simultaneously on the forearm and calf. Data

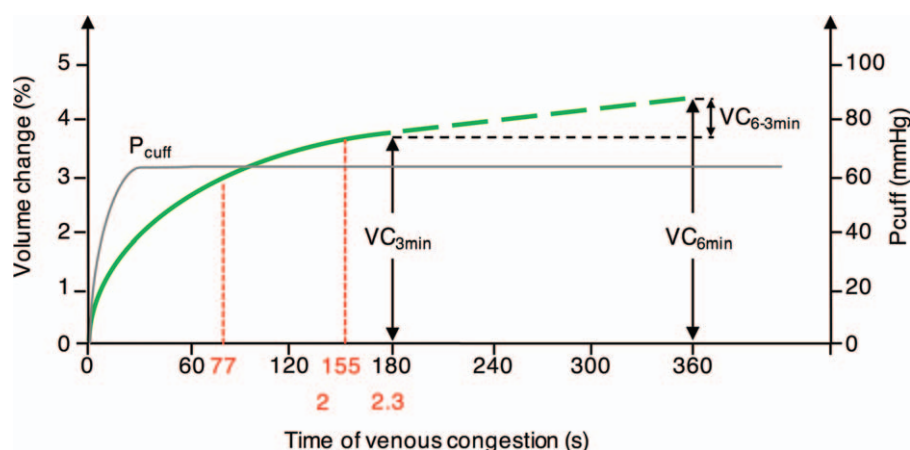


Figure 1. Venous congestion plethysmography was started by a single pressure increase and maintained at this level during the entire examination. Limb volume increases exponentially due to the rapid volume response (RVR). According to previous experiments, the time constant (τ) of RVR after a single pressure step was calculated at 77.3 ± 11.6 s.^[5] Our experimental protocol determined that the assessment of fluid filtration was started after 3 min (180 s) ensuring that after $\sim 2.3 \tau$ at least 90.3% of the RVR were completed. Fluid filtration was assessed by the difference of volume change (VC) between the third and sixth minutes during venous congestion (VC_{6-3min}).

acquisition and data processing was fully automated. VCP was started with a no pressure period while resting data were assessed. Resting data was recorded when 2 serial measures over 4 seconds did not differ. Thereafter, a single cuff pressure increase was performed to stop venous outflow and maintained at this level during the entire examination. Fluid filtration was assessed by the difference of volume changes (VC) of the limb between the third and sixth minutes during venous congestion (VC_{6-3min}) (Fig. 1). VC is the percentage increase of the cross section of forearm and calf at a predefined time point during venous congestion and is calculated by averaging the VC values during the last 5 seconds prior to the predefined time point.

An approach including a single pressure increase was chosen, as the duration of an examination with serial small pressure increments is in general 35 to 40 minutes, which demands more patient cooperation than we can expect in wake nonintubated patients after major surgery and is not always feasible during clinical routine on the ward. Irrespectively of a single pressure increase or serial small pressure increments, limb volume increases exponentially due to the rapid volume response (RVR) describing the change in volume of the blood vessels due to the compliance of the vessels and the surrounding tissues, followed by linear increase of limb volume due to the alteration in interstitial volume secondary to fluid filtration.^[5] According to previous experiments, the time constant (τ) of RVR after a single pressure step is significantly longer than after small pressure increments and was previously calculated at a mean 77.3 ± 11.6 seconds.^[5] In this regard, our experimental protocol determined that the assessment of fluid filtration was started after 3 minutes (180 seconds) ensuring that after 2.33τ at least 90.3% of the RVR were completed. This approach diminishes the risk of including the RVR component in the analysis of fluid filtration despite a single cuff pressure increase. Implausible values of VC_{6-3min} (negative values or values $>5\%$) were excluded from final analysis.

2.4. Clinical assessment of edema

Prior to the clinical assessment patients were positioned supine for 10 minutes. Patients were asked for edema as patient self-

reporting has been proven to be a reliable and accurate method of assessing edema and therefore can complement the physician's clinical assessment.^[12] The interrater variability was minimized by only 2 members of the study team performing the assessment. The clinical assessment for pitting edema was performed at 3 anatomical locations (the lower calf at 7 cm proximal to the midpoint of the medial malleolus, behind the medial malleolus, and the dorsum of the foot).

2.5. Statistical analysis

Because of limited sample sizes and nonnormal distributions of the observations, data were expressed as median (25%, 75% quartiles), or frequencies (%), respectively. Therefore, differences in continuous variables were tested using the Mann-Whitney *U* tests for independent groups.

Agreement of VC_{6-3min} between forearm and calf measurement sites was evaluated by the comparison of forearm and calf measurements of each patient during the perioperative course aggregated over the median and by Bland-Altman analysis for repeated measurements per patient. In Bland-Altman analysis the bias was defined as the mean of differences between the 2 methods. A linear mixed model with random effects was used to calculate the limits of agreement (LOA) with upper (bias + 1.96SD, ULOA) and lower (bias - 1.96SD, LLOA) limits.^[13] The percentage error was calculated as $1.96 \times SD$ of the bias / $(\text{mean}(VC_{6-3min\text{forearm}} + VC_{6-3min\text{calf}})/2)$.

Agreement of VC_{6-3min} between forearm and calf VC with respect to changes during the perioperative course was analyzed using the polar plot methodology and the direction of change analysis from a 4-quadrant plot.^[14,15] In polar plot analysis, agreement between the 2 measurement sites is shown by the angle from the polar axis. The mean polar angle (or angular bias) and the radial limits of agreement (RLOA), radial sector that contains 95% of the data points were determined. Acceptable agreement is generally defined as RLOA's lying within a sector of $\pm 30^\circ$.^[15] In the 4-quadrant plot, the concordance rate was calculated as the number of VC_{6-3min} values with the same directional change of both measurements sites in relation to the

total number of VC_{6-3min} values. Acceptable concordance was set at 90% to 95%.^[14]

Investigating the association of VC_{6-3min} of each measurement site with the presence of edema, a boxplot presentation including a gray zone approach was chosen.^[16] The gray zone was defined as 95% CI of the mean value of the best cutoff determined according to the Youden index within a receiver operating characteristic curve and conducted for a 1000 samples bootstrapped from the study population. According to the gray zone, the VC_{6-3min} values of the patients were grouped into 3 groups (below, into, and above the gray zone) for each measurement site. Then a logistic regression analysis for repeated measurements per patient was performed to assess the association of grouped VC_{6-3min} values of forearm and calf measurement site with respect to presence of edema.^[17] Odds ratios (OR) with 95% confidence interval (CI) were computed.

All numerical calculations were performed with IBM SPSS Statistics, Version 20, Copyright 1989, 2010 SPSS Inc and the R project for Statistical Computing, Version 3.0.2 (R-packages used: foreign, gplots, plotrix, MethComp, pROC, ROCR).

3. Results

Patient characteristics and intraoperative data of the study patients are shown in Table 1. Of the scheduled 240 measurements, a total of 208 measurements were performed in 30 patients: 2 patients discontinued the study and withdrew consent from POD1 (n=12); 4 patients declined the measurement at 1 time point during the postoperative course (n=8); 3 patients declined the measurement at 2 time points during the postoperative course (n=12). Another 36 measurements were excluded due to implausible values, while there were more implausible values obtained from the calf than the forearm (26 [21.6%] vs 10 [8.3%], $P=0.006$). Finally, 172 bedside measurements (94 measurements of the forearm and 78 measurements of the calf) were analyzed in 29 patients resulting in 74 paired measurements in the perioperative period.

Table 1

Patient characteristics.

Parameter	Study population (n=29)
Age, y	58 (52; 65)
Body mass index, kg/m	22.5 (20.8; 26.1)
American Society of Anesthesiology (ASA) status	
ASA physical status I, n, %	2 (6.9)
ASA physical status II, n, %	12 (41.4)
ASA physical status III, n, %	15 (51.7)
Chronic medications	
Beta blocker, n, %	3 (10.3)
Angiotensin converting enzyme inhibitors or angiotensin type 1 receptor antagonists, n, %	4 (13.8)
Statins, n, %	1 (3.4)
Calcium channel blocker, n, %	0 (0)
Diuretics, n, %	1 (3.4)
Pre-existing diabetes mellitus, n, %	1 (3.4)
Presence of ascites prior surgery, n, %	7 (24.1)
Presence of edema according to clinical examination	
Preoperative day, n, %	8 (27.6)
Postoperative day 1, n, %	14 (48.3)
Postoperative day 3, n, %	12 (41.4)
Postoperative day 5, n, %	6 (20.7)

Data are shown as median (25%; 75%) quartiles or as n (%) patients.

3.1. Agreement of VC_{6-3min} between forearm and calf measurement site

Perioperative values of forearm VC_{6-3min} were significantly higher than calf VC_{6-3min} (0.6 [0.4; 0.9] vs 0.4 [0.3; 0.6]%, $P=0.008$) (Fig. 2A).

Bland–Altman analysis including all perioperative measurements of VC_{6-3min} revealed a poor agreement between forearm and calf measurement site (bias of +0.23%; limits of agreement of –1.1% to 1.6%; and percentage error of 228%) (Fig. 2B). Polar plot analysis revealed a small bias of –2.5°, but showed wide radial limits of agreement (–81.9 to 76.8°) indicating an overall poor agreement of changes of VC_{6-3min} during the perioperative course between forearm and calf measurement site. A poor agreement of changes of VC_{6-3min} between both measurement sites was consistently shown by a low concordance rate of 56.7% in 4-quadrant plot (Fig. 2C and D).

3.2. Association of VC_{6-3min} obtained from forearm and calf measurement site with the presence of clinical edema

Forearm VC_{6-3min} was significantly higher in patients with the presence of clinical edema than in patients without signs of edema (0.7 [0.5; 1.0] vs 0.5 [0.4; 0.6]%, $P<0.001$) (Fig. 3A). In contrast, calf VC_{6-3min} did not differ in patients with and without edema (0.3 [0.2; 0.6] vs 0.5 [0.2; 0.6]%, $P=0.581$) (Fig. 3C). The gray zone calculated for forearm VC_{6-3min} was narrow with a range from 0.5% to 0.7%, while the gray zone of forearm VC_{6-3min} was wide ranging from 0.1% to 0.9%, respectively.

In this regard, compared with patients showing forearm VC_{6-3min} values below the gray zone (<0.5%), patients with forearm VC_{6-3min} values in the gray zone (0.5%–0.7%) had an odds ratio (OR) of 2.9 (95% CI 0.99–8.9; $P=0.051$) and patients with forearm VC_{6-3min} values above the gray zone (>0.7%) had an OR of 10.8 (95% CI 3.3–34.3; $P<0.001$) (Fig. 3B). According to the findings that calf VC_{6-3min} did not differ in patients with and without edema, there were no significant associations of VC_{6-3min} obtained from calf measurement site with clinical edema in logistic regression analysis (Fig. 3D).

4. Discussion

The principal findings of the study are that in nonsedated patients during the perioperative course the agreement of VC_{6-3min} obtained from forearm and calf measurement site was poor; and that forearm VC_{6-3min} was significantly higher in patients with the presence of clinical edema while calf VC_{6-3min} did not differ in patients with and without edema.

In recent years, microvascular fluid filtration has regained interest especially with focus on patients with sepsis, trauma or during and after major surgery.^[1,2] Further research in surgical patients is required to better understand fluid filtration during the perioperative period, which might have implications for treatment to enhance recovery after surgery. However, fluid filtration assessed by VCP can be obtained from forearm and calf measurement sites, while in many clinical situations there is reduced access to the patient often restricting the measurement site to patient's forearm. In this regard, it was uncertain if measurement sites of fluid filtration obtained by VCP at bedside are interchangeable in hospitalized patients.

In our study, agreement of fluid filtration between forearm and calf measurement sites was evaluated by the difference of both measurement sites (systemic bias) and by limits of agreement reflecting the variation of the difference of both measurement

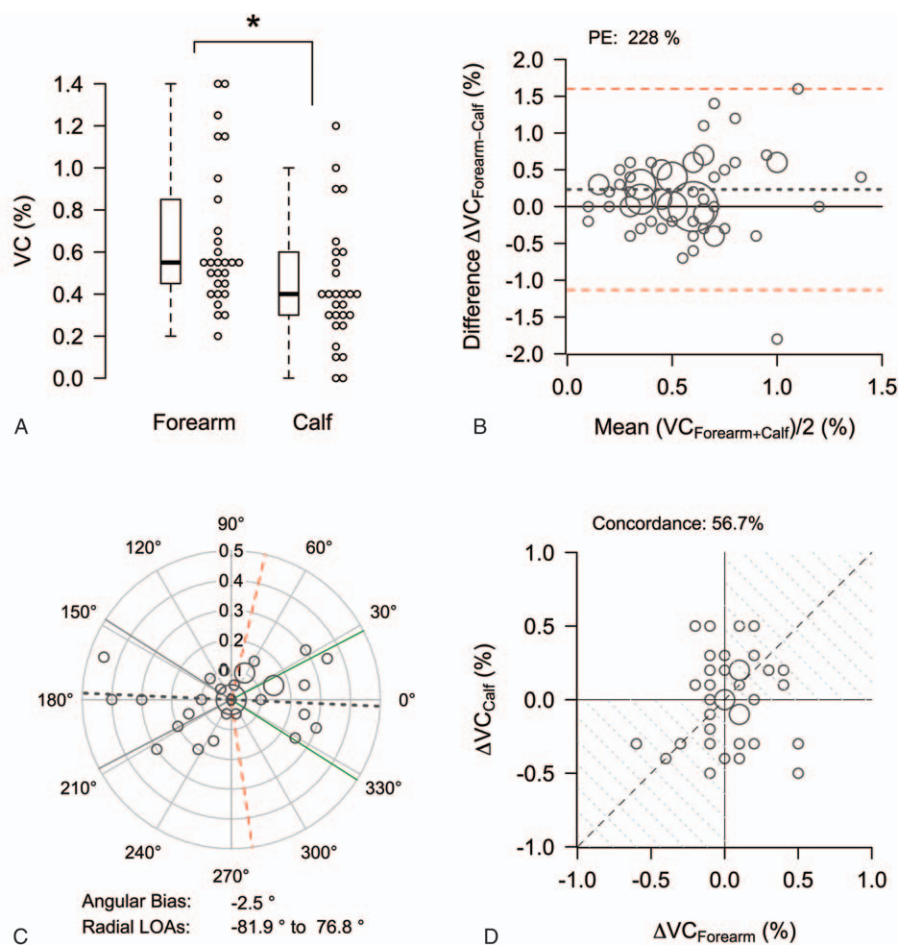


Figure 2. Agreement of VC_{6-3min} between forearm and calf measurement site: comparison of forearm and calf measurements of each patient during the perioperative course aggregated over the median (A); Bland-Altman plot for multiple measurements per patient assessing the agreement between forearm and calf measurement site (B); and Polar Plot analysis (C) and 4-quadrant plot (D) assessing agreement of changes of forearm and calf VC_{6-3min} during the perioperative course. Bias and limits of agreement (bias \pm 1.96SD) in Bland-Altman and Polar Plot presentation are visualized by gray and red dashed lines, respectively. In 4-quadrant plot the gray dashed line represents the line of identity. Regarding better visualization, the magnitude of the circles corresponds to the number of identical measurement values. PE=percentage error, VC_{6-3min} =volume change.

sites around the systemic bias. Both the comparison of forearm and calf measurements of each patient during the perioperative course aggregated over the median as well as Bland-Altman analysis for multiple measurements per patient showed that fluid filtration by VCP obtained from forearm was higher than obtained from the calf. In detail, our data show that forearm fluid filtration was about 33% higher than calf fluid filtration. These findings are consistent with previous studies indicating 38% and 39% higher fluid filtration obtained from forearm compared with calf measurement site in healthy volunteers.^[10,11] Formerly, it had been stated that the observed difference of fluid filtration between forearm and calf is attributed to different ratios of bone to soft tissue of both measurement sites.^[11] This conjecture was based on findings in subjects where fluid filtration of forearm and calf became more similar when expressing the fluid filtration per unit volume of soft tissue.^[11] However, experiments using magnetic resonance imaging showed that the difference in ratios of bone to soft tissue between forearm and calf is supposed to contribute only to a 10% greater fluid filtration in the forearm than in the calf.^[10] This fact was confirmed by measurements using dual-energy X-ray absorptiometry also indicating that the ratio of bone to soft tissue is supposed to only explain a difference of fluid filtration of 9.4%.^[18] In this regard, the difference in ratio

of bone to soft tissue cannot entirely explain the differences in fluid filtration found by our and former results. In general, the vasculature of the lower limb is exposed to higher blood pressures secondary to an increased hydrostatic pressure in the upright posture. In this context, the vasculature of the lower limb is supposed to preserve an adequate level of fluid filtration at higher transendothelial pressure differences compared with the upper limb. To date, there are no studies published that have investigated fluid filtration in subjects in upright posture. It has to be noted that our and former results, which indicated that forearm fluid filtration was higher than calf fluid filtration, were obtained in subjects in supine position. In this context, a higher fluid filtration in forearm than calf assessed in subjects lying supine is supposed to reflect a physiological adaption of vascular properties of the lower limb to prevent from edema formation in the upright posture that is not abrogated by resting in supine position. In this context, in healthy volunteers, who underwent 20 days of bed rest, differences of fluid filtration between forearm and calf were not neutralized despite for a long time unloading from gravitational forces.^[19,20] Furthermore, it has been shown that vascular responses to both endothelium-dependent and independent vasodilator agents are blunted in the leg compared with the arm, suggesting that the vasculature of the lower limb is

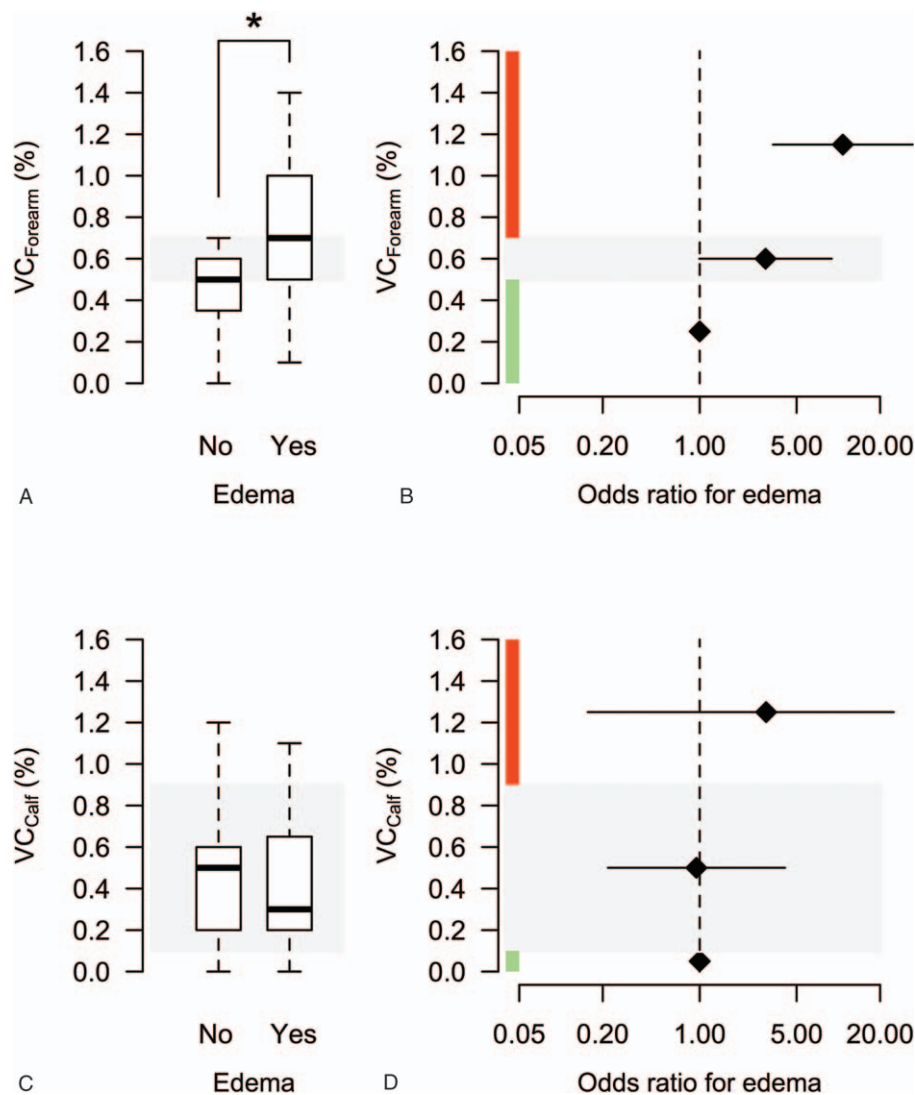


Figure 3. Association of VC_{6-3min} obtained from forearm and calf measurement site with clinical edema: boxplot presentation (including a gray zone) for the comparison of VC_{6-3min} in the presence or absence of clinical edema during the perioperative course (A, C); and results from the logistic regression analysis for repeated measurements per patient presented as odds ratios (with 95% CI) giving the association of grouped VC_{6-3min} values (below [green], into [gray], and above [red] the gray zone) of forearm and calf measurement site with respect to the presence of edema (B, D). CI=confidence interval, VC_{6-3min} =volume change.

preserving against a further increase of capillary hydrostatic pressure preventing from edema formation.^[21,22] In fact, from a rational view, differences of fluid filtration between forearm and calf measurement site found in supine healthy volunteers and supine perioperative patients are supposed to be attributed to physiological adaptations of the lower limb vasculature secondary to demands in the upright posture.

Bland–Altman analysis also revealed wide limits of agreement reflecting that the difference of both measurement sites had a large variation around the systemic bias. This finding was also observed when investigating the agreement of changes of fluid filtration during the perioperative course by Polar Plot and 4-quadrant analysis. Given that only forearm measurements were associated with the presence of edema during the perioperative course, it can be suggested that the poor agreement between forearm and calf measurement site is attributed to measurement errors of the leg measurement site in our study population. This is further supported by the fact that 22% of the leg measurements, but only 8% of the arm measurements had to be excluded due to

implausible values. In a recent study assessing fluid filtration only from leg measurements site in critical care patients, a similar substantial number of the leg measurements (28%) had to be excluded due to motion artifacts.^[9] Similar leg exclusion rates were reported in another study in patients with septic shock.^[8] However, in these studies, leg fluid filtration was found to be associated with the presence of edema and with the presence of sepsis despite the fact of high exclusion rates. The reason might be that most of these patients were intubated and sedated minimizing the risk of muscle movements during the VCP while our patients were awake. During VCP the patients are requested to remain absolutely still and it has been stated that minimal muscle movement or shivering may impair data acquisition.^[9] Furthermore, the leg positioning is less robust than the arm positioning, a priori bearing more risk for interference with minimal muscle movement or shivering. In this regard, in our awake patients, it is supposed that the lacking association of fluid filtration obtained from calf measurement site with the presence of edema might be due to measurement errors that could not be

detected during data exclusion, as they did not fulfill the criteria of implausible values.

The study has some limitations. In our study, an approach including a single pressure increase was chosen for VCP, as this approach allows a quick assessment and is therefore well tolerated in wake nonintubated patients during the perioperative course and is feasible during clinical routine on the ward. In this regard, although the assessment of fluid filtration was started after 3 minutes ensuring that at least 90.3% of the RVR were completed, it cannot be excluded that a potential residual RVR might have influenced the results. However, due to the association with edema shown for arm measurement site, a bias by residual RVR is assumed to be unlikely. Furthermore, subjects were female patients with epithelial ovarian cancer undergoing cytoreductive surgery. It cannot be excluded that pelvic surgical procedures may have influenced fluid filtration of the legs. Therefore, conclusions of this study must be limited to this patient group and cannot be presumed to other patient populations. Finally, patients with cancer are supposed to have alterations in endothelial permeability before surgery, whereas it is not known if alterations are equally pronounced in the systemic circulation.

In conclusion, forearm and calf measurement sites are not interchangeable when bedside assessing fluid filtration by VCP in awake and nonsedated perioperative patients. In awake patients, the leg measurement site has been shown to be interference-sensitive resulting in a substantial number of measurement errors whereas the arm measurement site has been shown more robust. Considering this error robustness and that only forearm fluid filtration was related to the presence of edema, the forearm measurement site should be chosen as the primary site for assessing fluid filtration by VCP in awake and nonsedated patients.

Acknowledgments

The authors thank all staff members of the Department of Gynaecology, European Competence Center for Ovarian Cancer, Charité—University Medicine Berlin, Campus Virchow-Klinikum, Germany for always being supportive when conducting their experiments on the ward.

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