What is the best method to determine excessive arm volume in patients with breast cancerrelated lymphoedema in clinical practice? Reliability, time efficiency and clinical feasibility of five different methods

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What is the best method to determine excessive arm volume in patients with breast cancer-related lymphoedema in clinical practice? Reliability, time-efficiency and clinical feasibility of five different methods

Abstract

Purpose: The aim of present study was to investigate the reliability, time-efficiency and clinical feasibility of five commonly used methods for assessing excessive arm volume in patients with breast cancer-related lymphoedema (BCRL).

Methods: Excessive arm volume was determined in 30 participants with BCRL by five different methods: traditional volumetry with overflow, volumetry without overflow, inverse volumetry, opto-electronic volumetry and calculated volume based on circumference measurements. To investigate intra- and inter-rater reliability, measurements were performed twice by the same assessor and once by a different assessor. Intraclass correlation coefficients (ICCs), standard errors of the measurement (SEMs) and systematic changes between the means were calculated. To determine time-efficiency, the mean set-up time, execution time and total time were examined for each method. Furthermore, eleven limitations regarding clinical feasibility were listed and scored for each method. Finally, an overall ranking score was determined between the methods.

Results: Intra- and inter-rater reliability ranged between strong and very strong. Calculated arm volume based on circumferences showed the highest intra- and inter rater ICCs of .987 and .984, respectively. Opto-electonic volumetry was the fastest method, representing a mean total time of 1 minute and 43 seconds for performing a bilateral measurement. The least limitations were reported on the calculated volume based on circumferences method.

Conclusions: In view of its excellent reliability, low error rate, low cost, few limitations, and relative time-efficiency, we recommend the calculated volume based on arm circumferences method as preferred method to use in clinical practice, for evaluating excessive arm volume over time.

Key Words: Breast Neoplasms – Lymphoedema – Assessment – Reliability - Time-efficiency - Feasibility

What is the best method to determine excessive arm volume in patients with breast cancer-related lymphoedema in clinical practice? Reliability, time-efficiency and clinical feasibility of five different methods

Running title:

Reliability, time-efficiency of five volume methods

Tessa De Vrieze[1,2], Nick Gebruers[2,3], Wiebren A.A. Tjalma[3,4,5], Ines Nevelsteen[6], Sarah Thomis[7], An De Groef[1], Lore Dams[1,2], Elien Van der Gucht[1,2], Jean-Paul Belgrado[8], Liesbeth Vandermeeren[8], Nele Devoogdt[1,9]

1. KU Leuven - University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium
2. University of Antwerp, Department of Rehabilitation Sciences and Physiotherapy, MOVANT, Antwerp, Belgium
3. University of Antwerp & Antwerp University Hospital, Multidisciplinary Oedema Clinic, Antwerp, Belgium
4. University of Antwerp, Department of Medicine, MIPRO, Antwerp, Belgium
5. Antwerp University Hospital, Multidisciplinary Breast Clinic, Antwerp, Belgium
6. UZ Leuven – University Hospitals Leuven, Multidisciplinary Breast Centre, Leuven, Belgium
7. UZ Leuven - University Hospitals Leuven, Department of Vascular Surgery and Department of Physical Medicine and Rehabilitation, Centre for Lymphoedema, Leuven, Belgium

8. Saint-Pierre University Hospital, Lymphology Clinic of Brussels & Université libre de Bruxelles, Lymphology Research Unit, Brussels, Belgium

9. UZ Leuven - University Hospitals Leuven, Department of Vascular Surgery and Department of Physical Medicine and Rehabilitation, Center for Lymphoedema, Leuven, Belgium

Corresponding author:

Tessa De Vrieze, Physical Therapist, Manual Therapist (corresponding author)

ORCID 0000-0002-5719-6169

1) Research Group for Rehabilitation in Internal Disorders

Department of Rehabilitation Sciences, KU Leuven

O&N IV Herestraat 49 3000 Leuven - box 1510

Tel.: +32 16 345005, tessa.devrieze@kuleuven.be

2) Research Group MOVANT

Department of Rehabilitation Sciences and Physiotherapy, University of Antwerp

Universiteitsplein 1 2610 Wilrijk

Tel.: +32 472 74 16 77, tessa.devrieze@uantwerpen.be

Abstract

Objective: To investigate the reliability, time-efficiency and clinical feasibility of five commonly used methods for assessing excessive arm volume in patients with breast cancer-related lymphoedema (BCRL)

Design: Cross-sectional study

Setting: University Hospitals Leuven, Belgium

Subjects: 30 participants with unilateral BCRL

Methods: Excessive arm volume was determined by five different methods: traditional volumetry with overflow, volumetry without overflow, inverse volumetry, opto-electronic volumetry and calculated volume based on circumference measurements. To investigate intra- and inter-rater reliability, measurements were performed twice by the same assessor and once by a different assessor. Intraclass correlation coefficients (ICCs), standard errors of the measurement (SEMs) and systematic changes between the means were calculated. To determine time-efficiency, the mean set-up time, execution time and total time were examined for each method. Furthermore, 12 limitations regarding clinical feasibility were listed and scored for each method. Finally, an overall ranking score was determined between the methods.

Results: Mean age was 65 (±8) years, mean body mass index was 28 (±4) kg/m^2. Intra- and inter-rater reliability ranged between strong and very strong. Calculated arm volume based on circumferences (mean excessive arm volume: assessor A: 477 (±367) ml; assessor B: 470 (±367) ml; assessor A (second time): 493 (±362) ml) showed the highest intra- and inter-rater ICCs of .987 and .984, respectively. Opto-electonic volumetry was the fastest method, representing a mean total time of 1 minute and 43 (±26) seconds for performing a bilateral measurement. The least limitations were reported on the calculated volume based on circumferences method (3 out of 12 limitations).

Conclusions: Calculated volume based on arm circumferences is the best measurement method for evaluating excessive arm volume over time in terms of reliability, low error rate, low cost, few limitations, and time spent.

Key words: Breast Neoplasms – Lymphoedema – Assessment – Reliability - Time-efficiency - Feasibility

Introduction

More than 16% of the women treated for breast cancer develops lymphoedema of the arm[1]. The evaluation of the treatment effect in both research and clinical practice is not possible without an accurate, valid and reliable method to determine arm size. Especially in clinical practice, it is crucial that this measurement tool is easy-to-use and rapid as well.[2, 3]

To date, a plethora of different measurement methods capable of determining arm size is available, such as several methods for water displacement[4-6], opto-electronic volumetry[7] and circumference measurements.[8] The traditional way of performing the water displacement method is to measure the overflow of water.[6] An alternative method for determining arm volume is to measure the shortness of water, called inverse water volumetry.[4] Furthermore, recently a volumetry method that does not make use of an overflow, named ValGrado by the developers[10], has been introduced and will be further referred to as volumetry without overflow. Opto-electronic volumetry, or perometry, is another valid measurement tool that showed to be accurate and reproducible in homogeneous geometric shapes.[11] Additionally, based on circumference measurements of the arm, the total arm volume can be calculated by using geometric formulas, such as the truncated cone formula.[12] Table 1 provides an overview of evidence found in literature with regard to reliability, time-efficiency and reported limitations of five commonly used measurement methods. All methods show good to very good intra-rater and inter-rater reliability for measuring arm volume. However, almost none of the studies report on reliability of the assessment of excessive arm volume. Additionally, only a few studies also investigated the measurement error of each method. Regarding time-efficiency, standardized studies investigating the time needed to perform a certain measurement, are lacking. A recent systematic review providing best evidence regarding which measurement method is most appropriate in measuring lymphoedema, concluded that information on feasibility is scarce.[9] A literature search regarding reported limitations of each of the methods, resulted in nine possible limitations (see Table 1).

In conclusion, although plenty of research is already published concerning reliability of different measurement methods separately, a clear overview and comparison of their utility (in terms of reliability, time-efficiency and clinical feasibility), between different variants of water displacement methods, opto-electronic volumetry and calculated volume by using a perimeter, is still missing.

Therefore, the aim of the present study was to investigate and compare the reliability, time-efficiency and clinical feasibility of five different and commonly used methods for determining excessive arm volume in patients with BCRL in clinical practice.

(Table 1)

Methods

This cross-sectional study is part of the EFforT-BCRL trial[30] for which approval was obtained by the Ethical Committee of the University Hospitals of Leuven (CME reference S58689, EudraCT 2015-004822-33, Clinicaltrials.gov NCT02609724). The study was conducted in accordance with the Declaration of Helsinki and is reported following the recommended STROBE guidelines for observational studies.

Participants

Between July and November 2017, participants of the EFforT-BCRL trial ware asked to contribute in this subtrial. Eligibility criteria were: 1) female/male patients with unilateral BCRL of the arm, 2) currently in the maintenance phase of the decongestive lymphatic therapy, 3) no known recurrence of cancer. Participants were excluded when they: 1) had solely hand oedema, and 2) had open skin lesions on one of their arms at the time of the testing. All participants received written and oral information by mail as well as by phone. All participants signed the informed consent document in the prior EFforT-BCRL trial.

Data collection and assessments

All assessments were performed at the department of Physical Medicine and Rehabilitation of the University Hospitals of Leuven. Excessive arm volume of all participants was determined by five different methods:

- traditional volumetry with overflow, in which the overflow of water is weighted[6];
- volumetry without overflow, in which the volume of the upward displaced water is weighted when submerging the limb in the recipient[10];
- inverse water volumetry, an alternative method for determining arm volume whereby the shortness of water is measured[4];
- opto-electronic volumetry (or perometry), a method that makes use of an optical-electronic infrared device to detect volume differences (without considering hand volume)[11]; and
- calculated volume based on circumference measurements, whereby total arm volume (without considering hand volume) can be calculated by using geometric formulas, such as the truncated cone formula. [12] This formula postulates that every section of the limb represents a perfect circle, and that the walls of the cone are rectilinear.

For each participant, the volume of both arms was measured. To determine the excessive arm volume, the volume of the non-oedematous arm was subtracted by the volume of the oedematous arm. Table 2 comprises a detailed overview of the five different measurement methods for assessing arm volume and excessive volume and their standardized procedures.

Descriptive data was collected by interviewing the participants and by consulting their medical record. For each participant, only one visit to the hospital was necessary to collect all data. Participants arrived 15 minutes prior to the start of the measurements at the hospital in order to stabilize skin temperature with room temperature.[30] In our study room, a constant temperature of 21°C was maintained. During this time, compression sleeves and jewelry on both arms were removed.

The estimated duration for a single execution of the five different measurements was 30 minutes (i.e. one assessment block). Since the execution of an assessment block was performed three times consecutively, the total duration of the investigation was approximately 1.5 hours per participant. The sequence of the five measurement methods in one assessment block varied between the different participants, however, within each participant the same sequence was maintained among the three executions. The order of measured sides during the measurements was chosen randomly. Prior to the assessments, three different 2-hour training moments were scheduled to guarantee standardization between assessors (TDV, LV), as well as three consecutive 1-hour training moments focused on time measurements between the persons registering the scores (SVDS, AVH, MB, TP).

To investigate intra-rater reliability, the first and the last assessment block were performed by the same assessor (TDV). To investigate inter-rater reliability, the second one was performed by a different assessor (LV). In order to obtain blinding of the assessors for previous test results, a different person registered the score. To preserve blinding for the reference point(s), after completing each assessment block consisting of the five methods, reference points were removed using alcohol wipes.

To provide an overview concerning time-efficiency of the five methods, a subdivision was made between: 1) the time needed to prepare the measurement and is reported as setup time, 2) the time needed for a bilaterally execution of the measurement and is reported as execution time, and 3) the total time required for the setup and execution of the measurement.

The setup of the measurement equipment was consistently prepared according to a predetermined and standardized protocol. Volumeters were filled with tepid water since literature showed that water temperatures across this range do not affect the density of water (and consequently, the weight of water measured), and do not cause vasodilatation/ vasoconstriction of the blood capillary system.[6, 26, 32] Setup time was determined for traditional volumetry with overflow, volumetry without overflow and inverse volumetry. Other methods did not require any preparation in advance (Table 2). Subsequently, execution of the five different methods was timed in a consistent and standardized manner as well. In Table 2, the timing protocol for each method in particular is described in more detail.

(Table 2)

Limitations regarding clinical feasibility of the different methods reported in literature (Table 1) were discussed by a team of experts in the field. Additionally, limitations reported by the experts retrieved from clinical experience were added to the list, after which all limitations were scored for each of the five measurement methods (yes/no). Two experts have many years of clinical and scientific experience in using the measurement methods (ND, NG), and the other expert has performed the assessments during the current study (TDV).

Finally, an overall comparison between the five methods regarding their reliability, time-efficiency and clinical feasibility is performed in order to provide an overview about the most appropriate method to use in clinical practice for measuring the excessive arm volume over time.

Data analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 24.0. The 0.05 level of significance was applied. Descriptive statistics for continuous values are presented as mean ±SD for normal distributed data and median and interquartile range for not normal distributed data. Categorical variables are presented as number and proportion (%).

Reliability of the volume measurements of the oedematous limb, the non-oedematous limb and of the excessive arm volume were analyzed. Intraclass correlation coefficients (ICCs) were used to examine intra-rater and inter-rater reliability between the different measurement occasions.[33] ICC estimates and their 95% confident intervals (CIs) were calculated based on a single rating (k=1), absolute agreement, two-way random-effects model.[34, 35] The ICCs were interpreted as follows: <.40 weak, .40 to .74 moderate, .75 to .90 strong and >.90 very strong[36, 37].

To interpret the magnitude of the within-subjects variation of the two scores, the standard error of measurement (SEM) was calculated using following formula: SEM = SD(difference)/(2)$^{0.5}$, where SD was the standard deviation of the volume differences between the two assessments.

To calculate systematic changes in the mean between two measurement occasions, paired samples t-tests were applied since the Shapiro-Wilk test revealed a mainly normal distribution of data.

A one-way ANOVA analysis was executed to demonstrate statistical significant differences among group-means, assisted with post hoc analyses for further evaluation.

Descriptive statistics on the reported limitations were performed to describe the clinical feasibility of each method.

Finally, data was used to compile a ranking table. Therefore, reliability of each method was based on the intra- and inter-rater ICC values of the excessive volume and was ranked between 1 (most reliable method) and 5 (least reliable method). The rating of time-efficiency was based on the total time, and consequently resulted in a ranking between 1 (most time-efficient method) and 5 (least time-efficient method). The rating of clinical feasibility was determined as the sum of scores on the reported limitations for each method. Based on this score, all methods were ranked between 1 (most feasible method) and 5 (least feasible method). Finally, based on the sum of the different scores on each item, the methods were ranked between 1 (most appropriate method) and 5 (least appropriate method).

Results

Thirty women were enrolled in this study. All measurements were completed in all 30 participants. Mean age was 65 (±8) years and mean body mass index (BMI) was 28 (±4) kg/m^2. An overview of the characteristics of the included subjects is provided in Table 3.

(Table 3)

Tables 4 and 5 list the intra-rater and inter-rater ICC values (with 95% CI), the SEMs (with 95% CI), and the mean volumes on each test occasion, supported with the outcomes of the paired samples t-tests.

- *Intra-rater reliability:*

  Taken into account the results considering the excessive arm volume, all methods showed satisfying ICCs, ranging from .777 to .987. Calculated arm volume based on circumferences showed the highest ICC of .987. Similar to the ICC results, calculated arm volume based on circumferences showed the lowest SEM, resulting in a variation of one test occasion to the other of 41.58ml.

- *Inter-rater reliability:*

  Likewise, considering the results regarding the excessive volume between the two arms, ICCs ranged between .791 and .984. Calculated arm volume based on circumferences showed the highest ICC of .984. Additionally, this method presented the lowest SEM, resulting in a test variation between two test occasions by different assessors, of 45.3ml.

(Tables 4 and 5)

An overview of the results regarding mean setup time, mean execution time and mean total time (±SDs) of the different measurement methods is given in Table 6. Additionally, a visual comparison of the results, assisted with the ANOVA post hoc outcomes, is illustrated in Figure 1. Regarding the ANOVA post hoc analyses, Games-Howell post hoc analyses were performed since equal variances were not assumed.

- *Setup time:*

  Volumetry without overflow showed to require the least time, with a mean setup duration of 4 minutes and 40 (±12) seconds. Mean setup time differed statistically significant between traditional volumetry with overflow and volumetry without overflow ($p<0.01$).

- *Execution time:*

  Mean bilateral execution time was lowest for volumetry without overflow (56 (±12) seconds). Mean execution time was highest for inverse volumetry (5 minutes and 34 (±210) seconds) ($p<0.01$).

- *Total time:*

  With regard to the time needed for both setup (if required) as well as a bilaterally execution of the measurement, opto-electonic volumetry turned out to be the fastest method, representing a mean time of 1 minute and 43 (±26) seconds. Every pairwise comparison of methods showed statistical significant differences between their means ($p<0.05$).

(Table 6)

(Figure 1)

Nine limitations regarding clinical feasibility that were listed in Table 1 were supplemented with following three limitations, retrieved from clinical experience: 1) the device is difficult to apply in patients with limited postural balance, 2) segmental measurements for evaluation of local changes are not provided, and 3) indirect measurement of volume (calculations need to be performed after the measurement). Finally, these 12 limitations were scored in Table 7. Least limitations were seen in the calculated volume based on circumferences method.

(Table 7)

A summarizing ranking table is presented in Table 8. Results revealed that calculated volume based on circumference measurements received the highest overall rank. Therefore, this method is considered as the most appropriate method to use in clinical practice based on our scored items (see Table 8).

(Table 8)

Discussion

In terms of reliability, low error rate, low cost, few limitations and time-efficiency, calculated volume based on arm circumferences is the best measurement method for evaluating excessive arm volume in patients with BCRL over time in clinical practice.

All five investigated methods showed good to very good **reliability**, which are comparable to previous results.[12, 14-17, 25] Nevertheless, it should be noted that previous results are mainly based on measurements executed on the oedematous limb or on a healthy limb. However, we preferred to perform measurements on both arms in order to determine and analyze the excessive arm volume, since it has the advantage to be able to correct for changes in muscle size and subcutaneous fat when monitoring long-term treatment effects. Limited reliability studies did also investigate the measurement error, and of those who did, only a few have reported the formula that was used.[12, 13]

Since the volumetry without overflow method has only recently been introduced[10], no previous publications regarding the clinimetric parameters of this method are available yet. When observing the results of this method in current study, one can notice a slight distinction with the other four methods due to a relatively lower intra- (.777) and inter-rater (.791) ICC of the excessive arm volumes, corresponding with a SEM of 146.36ml and 138.25ml, respectively. Nevertheless, these values still represent strong intra- and inter-rater reliability. A potential pitfall that can be causal for this variability, might be found in the accuracy of repeatedly indicating the same reference points before the measurement starts. The most important reference point is located in the elbow fold and is defined as the skin fold which is most centrally located in the elbow fold. Starting from this line, a proximal distance of 10 cm is measured to indicate the reference point required for measuring total arm volume. In our opinion, a difference in interpretation and perception between different assessors (and even within the same assessor) to define this most centrally located elbow fold, can contribute to this variability. As it was shown that volumes calculated from circumferences relative to anatomic (bony) landmarks are more accurate than those from segments using defined distances[12], an alternative approach in indicating reference points might be helpful to decrease this within-subjects as well as between-subjects variability.

This is the first study investigating **time-efficiency** of the different measurement procedures using a standardized protocol. Consequently, there is little information in literature available that allows us to compare our findings (Table 1). In the current study, opto-electronic volumetry showed the least total time required to complete a bilateral measurement (1min 42sec on average). Previous studies also mentioned opto-electronic volumetry being a quick device, taking only a few seconds[11, 14] to two minutes per measurement[24]. One study mentioned that the time required to complete volume measurements using a traditional volumetry device with overflow was 20 minutes[15], in contrast to the mean total time of 10 minutes 40 seconds in the current study. Furthermore, studies reported an average duration of 10 minutes for performing separate girth measurements after which the arm volume was calculated using the formula for a truncated cone.[15, 24] In the current study, the measurement lasted about 4 minutes and 24 seconds on average by using a perimeter. In the study of Damstra et al, volume measurements of both arms by making use of inverse volumetry required 5 minutes[4], which is remarkably lower than the time required in the current study (12min 55sec on average). However, information whether this time also included calibration time, was not provided. In the current study, the execution time of the inverse volumetry without the calibration time was 5 minutes 33 seconds on average, which would be comparable with the results of Damstra et al.[4] Another study reported a mean total time of 15 minutes, with most time spent on the preparation.[21]

Concerning **clinical feasibility**, there is no consistency found in literature. Moreover, a recent systematic review providing best evidence regarding which measurement method is most appropriate in measuring lymphoedema, concluded that information on feasibility is scarce.[9] Results of our ranking revealed that water displacement methods yield more practical limitations than calculated volume based on circumference measurements and opto-electronic volumetry.

Some study limitations should be mentioned. Although good to very good reliability was demonstrated in all five methods, the relatively small number of participants might have lowered the variability between participants. However, as stated by Shrout and Fleiss, researchers should try to obtain at least 30 heterogeneous subjects for reliability studies which was established in this study.[35]

Next, an opto-electronic volumetry device primary designed for lower limbs was used. However, to encounter this hindrance, a strict and standardized protocol regarding sitting posture and measurement procedure was carried out in order to provide unambiguous measurements of the upper limb.

Besides the mentioned limitations, this investigation contains several strengths. First, since we analyzed the reliability of the different methods by measuring both the oedematous and the non-oedematous arm, our results can be extrapolated to a patient population as well as to a healthy population or to a patient population without clinical representation of lymphoedema. Second, in order to investigate reliability and time-efficiency as accurate as possible, several training moments between assessors were organized ensuring standardization of the measurement procedure.

Third, to eliminate any risk for recall bias between the measurements, the assessor was supported by an independent assistant writing down the values and consequently, ensuring blinding of the data.

Calculated arm volume based on circumference measurements showed to be the most reliable and most feasible method to apply in clinical practice, in order to measure the excessive arm volume over time. Hereby, when measurements are performed by the same assessor, a test variation of more than 42ml should be considered as a change in excessive arm volume, exceeding the (potential) measurement error. In case the measurements are performed by different assessors, a test variation of more than 45ml exceeds the area of potential measurement errors. The device consists of materials with low costs, therefore it is easy to self-design a perimeter. Alternatively, it can be purchased as it is commercially available as well. For clinical centers having sufficient financial capacity, an opto-electronic volumeter can also be considered. However, a disadvantage of both methods is the fact that hand volume is not taken into account. Therefore, hand volume should be measured separately, for example by making use of a hand volumeter[38] or figure-of-eight method.[39, 40] In order to improve the hygienic conditions of the water volumetry method, an antiseptic (e.g. Chlorhexidine) or stabilized chlorine can be added to the water to disinfect the skin.

Since evidence is scarce regarding the recently introduced volumetry without overflow method, future research should focus on this technique. Results revealed that this is a very time-efficient water displacement method showing very strong intra- and inter-rater reliability for measuring the volume of an oedematous and non-oedematous limb, and strong intra- and inter-rater reliability for measuring the excessive arm volume. We believe that, with adjustment of the reference point's location, this method can be optimized which will result in smaller SEMs. Next, in current study we chose for a calculated volume based on circumference measurements method that made use of a perimeter instead of separate girth measurements (using a tapeline), since it comprises several advantages compared to separate girth measurements: 1) the device measures 11 circumferences at once by using only one reference point, resulting in quick measurements, 2) only one reference point needs to be marked and measured over time, which might result in smaller measurement errors, 3) since the tapelines are provided with weights (20g) at their end, the tension of the tapeline on the skin is standardized.[25] However, future studies should compare reliability and correlate these two measures, to investigate whether they could be used interchangeably. Furthermore, analysis of the data revealed that there is a remarkable difference in arm volume measured by the different methods at the oedematous limb, with opto-electronic volumetry representing the largest deviation. Consequently, further research regarding the criterion validity of these methods is warranted to ascertain whether the measured arm volume fully corresponds the actual arm volume.

Clinical messages

- Calculated arm volume based on circumference measurements showed to be the most reliable, the most feasible and a very time-efficient method to apply in clinical practice in patients with breast cancer-related lymphoedema, in order to measure the excessive arm volume over time.
- Since the calculated arm volume based on circumferences method does not include an evaluation of hand volume, therapists should measure this separately, for instance by making use of a hand volumeter[38] or figure-of-eight method[39, 40].

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Conflicts of interest

The authors declare that they have no conflict of interest.

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Tables

Table 1: Overview of studies investigating reliability and measurement variability (when indicated) of measurement methods quantifying arm volume of the oedematous limb

Traditional volumetry with overflow													
Reliability	**First author**	Chen et al 2008[13]	Deltombe et al 2007[14]	Galland et al 2002[15]	Gebruers et al 2007 (no lymphoedema)[6]	Gjorup et al 2010[16]	Karges et al 2003[17]	Megens et al 2001[2]	Meijer et al 2004[18]	Mori et al 2015[19]	Sander et al 2002[20]	Taylor et al 2006[12]	**RANGE**
	ICC intra	0.999	0.991	0.996	0.999	0.984	0.990	0.990	0.970-0.980	0.950	0.990	≥0.950	0.950-0.999
	ICC inter	0.990	0.987		0.999			0.990	0.910		0.990		0.910-0.999
	SEM (ml)	Intra 27.20 ml Inter 27.30 ml					11.46 ml (TEM*)				117.00 ml	66.50-81.70 ml	27.20 ml – 117.00 ml
Time-efficiency	**First author**	Galland et al 2002[15]											

	Time (min)	20 min											
Limitations	1) No visual information regarding the shape of the limb[20] 2) Once filled with water, material is not portable[2, 17, 26] 3) Problems with hygiene[26] 4) Not appropriate in subjects with wounds[16, 17, 22] 5) No evaluation of the proximal part of the upper arm[7]												
Volumetry without overflow													
Reliability	**First author**	*No publications yet*											
Time-efficiency	**First author**	*No publications yet*											
Limitations	1) No visual information regarding the shape of the limb[20] 2) Once filled with water, material is not portable[2, 17, 26] 3) Problems with hygiene[26] 4) Not appropriate in subjects with wounds[16, 17, 22] 5) No evaluation of the proximal part of upper arm[7]												
Inverse volumetry													
Reliability	**First author**	Beek et al 2015 *(no lymphoedema)*[21]	Damstra et al 2006[4]	Erends et al 2014 *(no lymphoedema)* [22]									**RANGE**

	ICC intra	0.990	0.997	0.990									0.990-0.997
	ICC inter		0.995										0.995
	SEM (ml)												
Time-efficiency	**First author**	Beek et al 2015[21]	Damstra et al 2006[4]										
	Time (min)	15 min	5 min										
Limitations	1) No visual information regarding the shape of the limb[20] 2) Material is not portable[2, 17, 26] 3) Problems with hygiene[26] 4) Not appropriate in subjects with wounds[16, 17, 22] 5) No evaluation of the proximal part of upper arm[7]												
Opto-electronic volumetry													

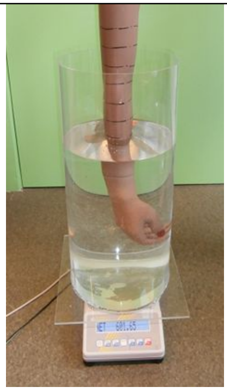
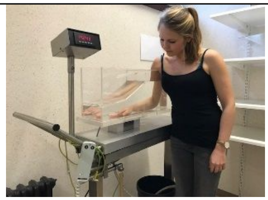
Reliability	**First author**	Adriaenssens et al 2013[23]	Deltombe et al 2007[14]										
	ICC intra	0.999	0.997										
	ICC inter		0.997										
	SEM (ml)												
Time-efficiency	**First author**	Deltombe et al 2007[14]	Sharkey et al 2018[24]	Stanton et al 1997[11]									
	Time (min)	Few seconds	2 min	Few seconds									
Limitations	1) Device takes a lot of space[27] 2) Expensive equipment[27] 3) The formula used to calculate the volume is unknown and can differ[28] 4) No evaluation of hand volume[4]												
Calculated volume based on circumference measurements													
Reliability	**First author**	Deltombe et al 2007[14]	Devoogdt et al 2010[25]	Galland et al 2002[15]	Gjorup et al 2010[16]	Karges et al 2003[17]	Taylor et al 2006[12]						**RANGE**
	ICC intra	0.958	0.997	0.995	0.998	0.990							0.958-0.998

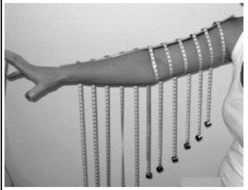
	ICC inter	0.937	0.994		0.997		0.970-0.990						0.937-0.997
	SEM (ml)		Intra 22.30 ml Inter 25.50 ml			Intra 9.35 ml TEM*)	Inter 64.5-71 ml						Intra 9.35-22.30 ml Inter 22.5-71.00 ml
Time-efficiency	**First author**	Devoogdt et al 2010[25]	Galland et al 2002 *(girth measurements with tapeline)[15]*	Sharkey et al 2018[24]									
	Time (min)	5 min	10 min	10 min									
Limitations	1) No evaluation of hand volume[4]												

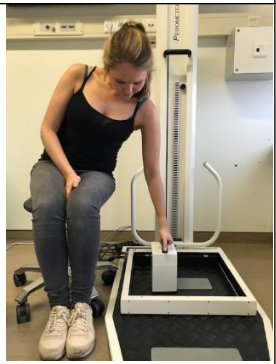
Note: * outcome is mentioned as TEM (absolute technical error of measurement); no formula was presented

Table 2. Protocol: overview of the five measurement methods and procedures

Assessment	Picture	Material	Reference points	Method		Outcome
				Setup	Procedure	
Traditional volumetry with overflow[6]	 *(with permission illustration from Gebruers et al 2007[6])*	Cubically shaped tank with overflow (18x18x76 cm) filled with tepid tap water of 20-30°C, chair, recipient placed on electronic weighing balance with 0.1g accuracy (KERN 572) on top of a platform of 25 cm height, skin pencil, chair or stool.	Half the distance between acromion and proximal edge of epicondylus lateralis (elbow flexed in 90° whilst marking reference point).	Place a recipient on a scale underneath the overflow. Fill the tank with water until the level of the overflow has reached and flows out. When the water stops dripping (frequency $\leq$ 1 drop per second), calibrate the scale (= 0g). Subject is sitting down next to the tank.	Extra water is added to the tank until the water level enters the overflow. During the time water is dripping, reference points are marked. Once the water stops to drip, the scale is tared. Subject lowers the arm into the tank until the water level reaches the marked reference point. The limb needs to be kept straight and perpendicular to the surface, with the palm of the hand placed against the edge of the volumeter. When the limb reaches the reference point, the position has to be maintained until the water stops dripping with frequency $\leq$ 1 drop per second. Read the weight of the water in the recipient.	Weight of the displaced water (g). Comparison left/right. Measurement of excessive volume of the whole arm = (volume oedematous limb – non-oedematous limb).
				Setup time= from setup till the water level in the tank reached the overflow.	Execution time= started with adding some extra water to the tank before finally taring the scale and ended when water of the overflow dripped with frequency $\leq$ 1 drop per second, after lowering the limb.	Setup time, execution time and total time (= setup time + execution time) (seconds).

Volumetry without overflow[10]		Cylinder filled with tepid tap water of 20-30°C, placed on weighing balance with 0.1g accuracy (KERN 572); both are placed on top of a platform of 25 cm height. Weighing balance is connected with 'Matlab' software programme on laptop, skin pencil.	10 cm proximal to the middle skinfold of the elbow crease.	Place the cylinder on a scale. Tare the scale. Subject is positioned in standing beside the cylinder.	Perpendicular to the water surface, subject lowers the arm into the cylinder until the water level reaches the marked reference point. Subject is given attention not to touch the border of the cylinder. Once the water level equals the level of the reference point on the upper arm, the assessor clicks on the assessment button; software programme performs 10 volume measurements and calculates mean volume (Volume of upward displaced water = Mass of water/ density of water, density of water with T° between 20-30°C is 1); a signal is given if mean volume or its standard deviation is outside of preset range.	Weight of the upward displaced water (g). Comparison left/right. Measurement of excessive lymphoedema volume whole arm = cfr. Supra.
				Setup time= from setup till the water level in the tank reached a level of 15cm below the upper edge (= arbitrary chosen to preserve standardization).	Execution time= timed in two phases: 1) application of reference points 2) started from lowering the arm in the tank until predefined reference point was reached and the weight was shown on the computer screen.	Setup time, execution time and total time (= setup time + execution time) (seconds).
Inverse volumetry[4]		Tank filled with tap water of 28°C standing on a weighting device, based on the metal bending principal.	No reference point.	Calibration procedure: Fill the tank with water until the water reaches the overflow. When the water stops dripping at a frequency ≤ 1 drop per second, calibrate to zero and drain	Subject places the olecranon in the corner at the opposite side of the tank, elbow flexed in 90°, pronation of the forearm, extension of the fingers. Assessor fills the tank until the water reaches the overflow. When the water stops dripping at a frequency ≤ 1 drop	Weight of the added water (g). Comparison left/right. Measurement of excessive lymphoedema volume whole arm = cfr. Supra.

				the water. This procedure needs to be performed only once daily. Measurement procedure: Subject is positioned in standing beside the tank. Adjust the height of the tank until subject is standing comfortable. Setup time= from filling the water tank till end of calibration.	per second, the arm is removed from the tank. The display of the weighting device shows the shortness of water compared with the initial situation. Execution time= started with placing the arm in the tank and ended when water of the overflow dripped with frequency ≤ 1 drop per second.	Setup time, execution time and total time (= setup time + execution time) (seconds).
Calculated volume based on circumferences[25]	 *(with permission illustration from Devoogdt et al 2010[25])*	Perimeter; which is a flexible stainless steel bar with a tapeline fixed every 4cm and a weight of 20g at the end, skin pencil, chair, table with adjustable height.	Proximal border of the olecranon.	Subject is in sitting position with 90° anteflexion of the arm, straight elbow and hand supported on table.	Arm circumferences measured at olecranon and at 4, 8, 12, 16 and 20 cm proximal and distal of olecranon. First, the reference point at the upper border of the olecranon. The bar was placed on the dorsal side of the arm: the middle tapeline was placed distal of the reference point perpendicular to the axis of the arm. The other tapelines were placed around the lower arm, also perpendicular to the axis of the arm. Then the circumference at each point was recorded. Afterwards, all tapes except the middle one were removed, and this procedure was repeated for the upper arm[25]	Volume of an arm segment of 4cm = $4 \times (C_1^2+C_1C_2+C_2^2)/12\pi$, where C_1 is the upper circumference and C_2 is the lower circumference of each segment[32] Calculated volume of whole arm = sum of the volume of all segments of the arm Comparison left/right. Measurement of excessive lymphoedema volume whole arm = cfr. Supra.

				No setup time.	Execution time= started with application of the reference point and ended after recording all circumferences of both arms.	Execution time (= total time) (seconds).
Opto-electronic volumetry[11]		Opto-electronic volumetry device (Perometer®) with a vertical arm, a portable block with handle on top of it, computer provided with 'PeroPlus' software (Pero-System Messgeräte GmbH, Wuppertal, Germany), chair or stool The Perometer consists of a vertically movable frame equipped with infrared light emitters and receptors. The infrared light beams are interrupted by the introduction of the arm into the frame[23]. By moving the frame along the long axis of the arm, a measure is automatically performed every 4.7	No reference point.	Subject is in sitting position next to the device. Hand of the subject is placed on a handle block which position remained unchanged during the entire measurement. The wrist stays in neutral position with closed and connected fingers and the thumb facing forward. The elbow is straight and the armpit is located just above and perpendicular to the ipsilateral border of the frame. No setup time.	Subject keeps a fixed position with the arm straight. Assessor moves the handle of the Perometer slowly up until the frame reaches the armpit, then moves slowly back down; a signal is given when the axilla (moving up) and the floor (moving down), are reached. Execution time= started with providing the instructions how to sit down in a correct and predefined starting position, and ended when the software program finished processing the data. Time to open the program (PeroPlus) is included in the execution time.	Volume of the limb in ml. Comparison left/right. Measurement of excessive lymphoedema volume whole arm = cfr. Supra. Measurement starts for every subject at a height of 58 cm (level of the wrist) end is ended at the corresponding height when the frame reaches the armpit. Subsequently, arm volume is calculated for these measures. Execution time (= total time) (seconds).

		mm[24] for a distance which is varying per subject, according to the individual arm length.				

Table 3. Characteristics of the included subjects (n=30)

Descriptives	
Variable	**Outcome** **Mean (SD)**
Age (y)	65 (8)
Body Mass Index (kg/m^2)	28 (4)
Duration lymphoedema (mo)	74 (44)
Frequencies	
Variable	**Outcome** **N (%)**
Lymphoedema stages	
stage I	3 (10%)
stage IIa	18 (60%)
stage IIb	9 (30%)
Location of lymphedema	
Lower arm	14 (53%)
Upper arm	0 (0%)
Total arm (lower arm + upper arm)	16 (47%)
Breast surgery	
Mastectomy	21 (70%)
Breast-conserving surgery	9 (30%)
Axillary lymph node clearance	
SLNB	1 (3%)
ALND	29 (97%)
Surgery on the dominant side	17 (57%)
Radiotherapy	30 (100%)
Chemotherapy	24 (80%)
Antihormonal therapy	27 (90%)
Target therapy (Herceptin)	6 (20%)

Abbreviations: y= years, kg= kilogram, m^2= square meters, mL= milliliter, mo= months, lymphoedema stages as described by the International Society of Lymphology (i.e. Stage I = Accumulation of interstitial fluid, with reduction by elevation. At this stage the oedema can be pitting. / Stage IIa = Swelling disappears barely by elevation, the oedema is clearly pitting. / Stage IIb = Pitting is clearly present by fibrotic formations in the oedema), SLNB = sentinel lymph node biopsy, ALND = axillary lymph node dissection

Table 4. Intra-rater reliability (n= 30)

	Method	First assessment (assessor A) Mean volume (SD; Min-Max)	Second assessment (assessor A) Mean volume (SD; Min-Max)	ICC (95% CI)	SEM (95% CI)	Paired samples T-Test P-value
Oedematous limb	Traditional volumetry with overflow	2662.64 (384.63; 1692.4-4401.3)	2681.16 (400.72; 1646.5-4389.8)	.950 (.899 - .976)	87.80 (-153.58 – 190.62)	0.643
	Volumetry without overflow	2253.21 (515.69; 1463.1-4401.3)	2246.16 (501.41; 1401.5-3287.7)	.950 (.898-.976)	113.72 (-216.3 – 229.46)	0.827
	Inversed volumetry	3160.4 (653.85; 2033-4760)	3166.23 (705.58; 1945-4672)	.979 (.957-.990)	98.5 (-187.23 – 198.89)	0.823
	Opto-electronic volumetry	5245.47 (747.32; 4140-7048)	5197.37 (729.05; 4084-6921)	.972 (0.941-.986)	123.52 (-194 – 290.2)	0.137
	Calculated arm volume based on circumferences	3000.88 (764.12; 1911.9-4727.6)	3016.16 (769.97; 1895.9-4776.2)	.999 (.997-.999)	24.26 (-40.26 - 54.82)	0.309
Non-oedematous limb	Traditional volumetry with overflow	2180.99 (534.31; 1337.5-3720.6)	2139.78 (537.86; 1359.9-3689.8)	.983 (.960-.992)	69.90 (-95.79 – 178.21)	0.019*
	Volumetry without overflow	1816.66 (332.32; 1193.0-2623.0)	1817.93 (351.28; 1173.5-2654.2)	.985 (.968-.993)	41.86 (-80.78 – 83.32)	0.910
	Inversed volumetry	2635.97 (552.95; 1655-4150)	2614.07 (587.52; 1624-4231)	.991 (.980-.996)	54.10 (-84.13 – 127.93)	0.128
	Opto-electronic volumetry	4694.6 (551.47; 3832-6128)	4658.9 (575.43; 3685-6333)	.961 (.921-.981)	111.27 (-182.39 – 253.79)	0.219

	Calculated arm volume based on circumferences	2531.95 (564.85; 1547.3-4069.8)	2523.11 (584.37; 8.8)	.995 (.990-.998)	40.63 (-70.80 – 88.48)	0.404
Excessive volume	Traditional volumetry with overflow	481.65 (384.63; -56.9-1498.2)	541.38 (400.72; -307.5-1195.3)	.813 (.646-.906)	169.81 (-273.09 – 392.55)	0.179
	Volumetry without overflow	419.07 (330.83; -128.6-1285.7)	428.7 (289.04; -33.8-1227.0)	.777 (.582-.888)	146.36 (-277.24 – 296.5)	0.803
	Inversed volumetry	524.43 (355.2; -140-1159)	552.17 (378.95; -195-1593)	.922 (.843-.962)	102.52 (-173.2 – 228.68)	0.315
	Opto-electronic volumetry	550.87 (415.75; -201-1420)	538.47 (366.25; -207-1308)	.921 (.842-.962)	109.90 (-203.00 – 227.80)	0.670
	Calculated arm volume based on circumferences	476.93 (367.31; -126.8-1345.3)	493.05 (361.99; -28.1-1454.7)	.987 (.973-.994)	41.58 (-65.37 – 97.61)	0.130

Abbreviations: SD= standard deviation, ICC= intraclass correlation coefficient, CI= confidence interval, SEM= standard error of measurement, * corresponds with p-value <.05, ** corresponds with p-value <.01

Table 5. Inter-rater reliability (n= 30)

	Method	**First assessment (assessor A)** **Mean volume (SD; Min-Max)**	**Second assessment (assessor B)** **Mean volume (SD; Min-Max)**	**ICC (95% CI)**	**SEM (95% CI)**	**Paired samples T-Test** **P-value**
Oedematous limb	Traditional volumetry with overflow	2662.64 (384.63; 1692.4-4401.3)	2647.33 (708.74; 1596.4-4436.1)	.954 (.907-.978)	117.25 (-245.50 – 214.12)	0.694
	Volumetry without overflow	2253.21 (515.69; 1463.1-4401.3)	2228.16 (488.66; 1149.6-2901.4)	.980 (.957-.990)	71.02 (-114.15 – 164.25)	0.452
	Inversed volumetry	3160.4 (653.85; 2033-4760)	3195.97 (692.24; 1934-4632)	.974 (.947-.988)	108.53 (-177.14 – 248.28)	0.206
	Opto-electronic volumetry	5245.47 (747.32; 4140-7048)	5062.07 (720.13; 4081-6676)	.949 (.504-.986)	165.70 (-141.37 – 508.17)	<0.001**
	Calculated arm volume based on circumferences	3000.88 (764.12; 1911.9-4727.6)	2942.47 (732.58; 1861.4-4608.4)	.993 (.921-.998)	62.61 (-56.31 – 189.13)	<0.001**
Non-oedematous limb	Traditional volumetry with overflow	2180.99 (534.31; 1337.5-3720.6)	2148.99 (525.8; 1370.7-3686.9)	.984 (.964 - .992)	67.05 (-99.41 – 163.41)	0.068
	Volumetry without overflow	1816.66 (332.32; 1193.0-2623.0)	1852.64 (394.29; 1149.6-2901.4)	.930 (.859-.966)	96.12 (-152.42 – 224.38)	0.354
	Inversed volumetry	2635.97 (552.95; 1655-4150)	2614.8 (565.49; 1521-4161)	.994 (.987-.997)	43.32 (-6373 – 106.07)	0.054
	Opto-electronic volumetry	4694.6 (551.47; 3832-6128)	4537.03 (534.1; 3743-6151)	.934 (.377-.982)	139.44 (-115.74 – 430.88)	<0.001**

	Calculated arm volume based on circumferences	2531.95 (564.85; 1547.3-4069.8)	2473.23 (545.88; 1516.7-3910.9)	.986 (.931 - .995)	65.71 (-70.07 – 187.51)	<0.001**
Excessive volume	Traditional volumetry with overflow	481.65 (384.63; -56.9-1498.2)	498.34 (354.15; -77.9-1293.3)	.861 (.729-.931)	137.72 (-253.24 – 286.62)	0.646
	Volumetry without overflow	419.07 (330.83; -128.6-1285.7)	375.53 (274; 1149.6-2901.4)	.791 (.606 – .895)	138.25 (-227.44 – 314.52)	0.520
	Inversed volumetry	524.43 (355.2; -140-1159)	581.17 (378.95; -20-1494)	.909 (.810-.957)	110.73 (-160.30 – 273.78)	0.046*
	Opto-electronic volumetry	550.87 (415.75; -201-1420)	525.03 (399.14; -229-1358)	.949 (.897-.975)	92.01 (-151.51 – 206.19)	0.285
	Calculated arm volume based on circumferences	476.93 (367.31; -126.8-1345.3)	469.24 (367.31; -88.7-1373.2)	.984 (.967-.992)	45.3 (-81.11 – 96.49)	0.523

SD= standard deviation, ICC= intraclass correlation coefficient, CI= confidence interval, SEM= standard error of measurement, * corresponds with p-value <.05, ** corresponds with p-value < 0.01

Table 6. Setup time, mean execution time and mean total time of five different measurement methods (n= 30)

Measurement method	Mean setup time (SD) in seconds	ANOVA p-value	Mean execution time (SD) in seconds	ANOVA p-value	Mean total time (SD) in seconds	ANOVA p-value
Traditional volumetry with overflow	444.00 (11.51)[a]	P<.01	275.80 (89.56)[c]	P<.01	640.53 (89.11)[f]	P<.01
Volumetry without overflow	280.00 (16.80)[b]		55.67 (11.57)[d]		335.67 (11.57)[f]	
Inverse volumetry	362.00 (69.35)		333.70 (209.56)[c]		775.00 (212.57)[f]	
Opto-electronic volumetry*			102.67 (26.02)[e]		102.67 (26.02)[f]	
Calculated arm volume based on circumferences			264.13 (26.53)[c]		264.13 (26.53)[f]	

* Time to open the program (PeroPlus) is included in the execution time

[a] statistical significant difference with volumetry without overflow (p <.01)

[b] statistical significant difference with traditional volumetry with overflow (p <.01)

[c] statistical significant differences with opto-electronic volumetry and volumetry without overflow (p <.01)

[d] statistical significant differences with inverse volumetry, opto-electronic volumetry and calculated arm volume based on circumferences (p <.01)

[e] statistical significant differences with traditional volumetry with overflow, volumetry without overflow, inverse volumetry and calculated arm volume based on circumferences (p <.01)

[f] every pairwise comparison of methods showed statistical significant differences between their means (p <.05)

Table 7. Details regarding the scoring procedure on clinical feasibility

		Traditional volumetry with overflow	Volumetry without overflow	Inverse volumetry	Opto-electronic volumetry	Calculated volume based on circumferences
Clinical feasibility	**Limitations** Outcome *(0= no limitation, 1= limitation)*					
	No visual info shape limb	1	1	1	0	1
	Not portable	1	1	1	1	0
	Problems with hygiene	1	1	1	0	0
	Not appropriate when having wounds	1	1	1	0	0
	No evaluation of proximal part upper arm	1	1	0	0	0
	Difficult to apply with limited postural balance	0	1	0	0	0
	Extensive device	0	0	1	1	0
	Expensive device/procedure (>3000 euros)	0	0	1	1	0

	No segmental evaluation of limb	1	1	1	0	0
	Formula for calculating volume is unknown	0	0	0	1	0
	No evaluation of hand volume	0	0	0	1	1
	Indirect volume measurement	0	0	0	0	1
	Total score	6	7	7	5	3
	Ranking clinical feasibility	**3**	**4**	**4**	**2**	**1**

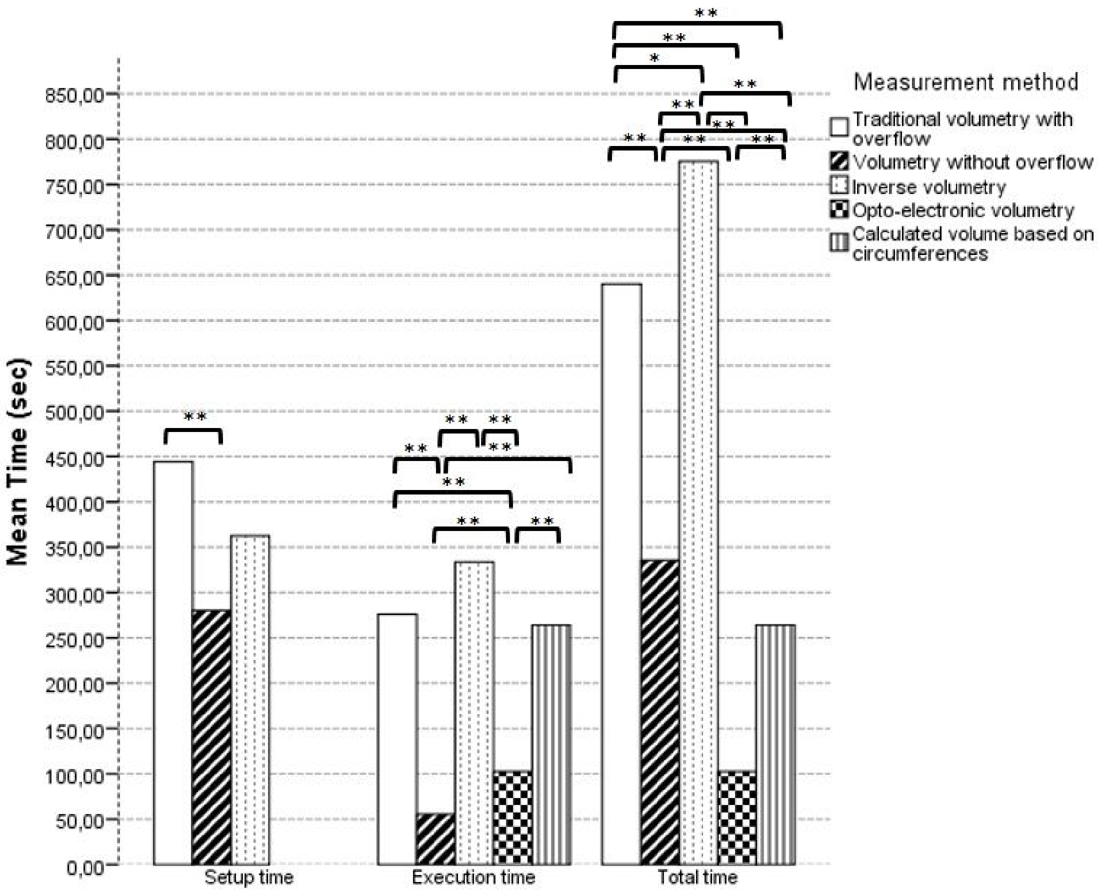
Table 8. Summary table with ranking of the five measurement methods regarding reliability (ICC), time-efficiency and clinical feasibility

		Traditional volumetry with overflow	Volumetry without overflow	Inverse volumetry	Opto-electronic volumetry	Calculated volume based on circumferences
Reliability	**ICC[a]** Outcome *(intra/inter)*	Intra: .813 Inter: .861	Intra: .777 Inter: .791	Intra: .922 Inter: .909	Intra: .921 Inter: .949	Intra: .987 Inter: .984
	Ranking	**4**	**5**	**3**	**2**	**1**
Time-efficiency	Outcome *(total time)*	640.53 seconds	335.67 seconds	775 seconds	102.67 seconds	264.13 seconds
	Ranking	**4**	**3**	**5**	**1**	**2**
Clinical feasibility	**Limitations** Outcome *(total score)*	6	7	7	5	3
	Ranking clinical feasibility	**3**	**4**	**4**	**2**	**1**
Total score		*11*	*12*	*12*	*5*	*4*
TOTAL RANKING		**3**	**4**	**4**	**2**	**1**

[a]Note: presented inter- and intra- rater ICC values are based on excessive volume results

Figures

Figure 1. Comparison of setup time, mean execution time and mean total time of five different measurement methods assisted with ANOVA post hoc analyses (n= 30)



* statistical significant difference between the mean times of both methods ($p<.05$)
** statistical significant difference between the mean times of both methods ($p<.01$)
Note: Games-Howell post hoc analysis was applied