

Methods for Simulating Hemodynamic Changes Resembling Deep Vein Thrombosis via External Pressure-Induced Stenosis

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Abstract

Purpose: Deep vein thrombosis (DVT) is a common cardiovascular disease posing the risk of pulmonary embolism. Current clinical DVT detection methods, ultrasound and contrast venography, are reliable, but ultrasound requires a skilled healthcare professional, while invasive venography involves exposure to ionizing radiation, making them unsuitable for continuous monitoring. Continuous monitoring could improve early DVT detection, especially in high-risk patients. Venous occlusion plethysmography (VOP) is a non-invasive method that could be suitable for operator-independent continuous monitoring. However, developing new diagnostic methods is demanding due to regulations related to clinical studies, challenges in patient recruitment, and increased risks when involving fragile study subjects. This study aims to evaluate methods of simulating DVT on healthy volunteers to reduce the need for patient involvement in pilot-phase studies. **Methods:** Data was collected from twenty healthy volunteers using the commercial VasoScreen 1000-4000 system. Varying levels of stenosis were induced by applying external pressure to mimic hemodynamic changes resembling DVT. Two simulation methods were evaluated: manual compression of the femoral vein using an ultrasound transducer, and compression of the thigh using a pressure cuff. **Results:** Both simulation methods demonstrated changes in the morphology of collected biosignals and produced statistically significant differences in various parameters. The smallest change relative to standard VOP was observed with manual compression-based simulation, whereas larger changes were achieved with cuff-based simulation by increasing the pressure. **Conclusion:** The cuff-based simulation allows simulation of hemodynamic changes resembling DVT with a varying degree of stenosis, whereas manual compression produces small hemodynamic changes with unreliable pressure control.

Keywords: Deep vein thrombosis, Venous occlusion plethysmography, Impedance plethysmography, Hemodynamics

1 Introduction

Deep vein thrombosis (DVT) is a common cardiovascular condition in which a blood clot or a thrombus forms in the deep veins [1]. Its annual incidence is approximately 90 cases per 100 000 individuals in Western countries [2]. Thrombi most commonly form in the deep veins of the lower extremities [1], whereas only approximately 10% of cases occur in the upper extremities [3]. Recurrent thrombosis and post-thrombotic syndrome usually reduce the quality of life and are associated with morbidity due to discomfort symptoms, such as pain, swelling, and redness of the limb [4]. DVT also carries the risk that a clot may detach from the vein wall, travel, and obstruct the pulmonary arteries [5]. This highly fatal complication is known as pulmonary embolism (PE); together with DVT, it constitutes the venous thromboembolism disorders, which are the third most common cardiovascular disease after heart attacks and stroke [1, 6].

Although contrast venography has traditionally been the gold standard for diagnosing DVT [7, 8], it has largely been replaced in clinical practice by venous ultrasound due to its invasive nature [7]. Therefore, venous ultrasound as a non-invasive method is currently the standard imaging test for diagnosing patients suspected of having acute DVT [9]. However, ultrasound is time-consuming and technically demanding, requiring a skilled healthcare professional, whereas contrast venography is not only technically demanding but also invasive and involves exposure to ionizing radiation [7, 8, 10]. Due to these disadvantages, the current methods are not applicable for continuous monitoring and point-of-care. This also limits early diagnosis, because DVT is often asymptomatic and the patient is usually diagnosed only after the onset of the symptoms [1]. In up to two-thirds of DVT cases, PE is the first symptom [8]. Only through early diagnostic and treatment, the morbidity of DVT and risk of pulmonary embolism can be reduced [1]. Therefore, new diagnostic tools are needed for continuous monitoring of DVT at the point of care, especially in high-risk patients.

Venous occlusion plethysmography (VOP) is a simple, non-invasive method for assessing DVT. The method relies on inducing changes in venous blood volume by temporarily occluding the thigh veins with a pneumatic cuff and measuring these changes over the release of the occlusion using a plethysmogram [11]. Strain gauges [12], air cuffs [13], or electrical impedance [14, 15] can be used for the plethysmographic measurement. By integrating portable impedance plethysmography sensors into wearables, operator-free continuous monitoring of DVT at the point-of-care would be possible to implement in high DVT risk patients [16]. However, developing new diagnostic methods is demanding due to regulations related to clinical studies with patients, challenges in patient recruitment, and potentially increased risks when involving fragile study subjects. Therefore, feasible methods for simulating hemodynamic changes resembling DVT could reduce the need for patient involvement in pilot-phase studies.

A limited number of approaches for simulating hemodynamic changes resembling DVT using external pressure-induced stenosis have been proposed in the literature. A recent approach by Eitminavičius et al. [17] applies targeted external pressure with an ultrasound transducer during the VOP measurement at two anatomical locations, the popliteal and femoral veins, located at the posterior knee and the inner thigh. These locations were selected due to their accessibility and the clinical relevance of proximal DVT. The use of ultrasonography enables estimation of the stenosis level during simulation. It also allows for a more targeted pressure application. The induced stenosis levels, monitored by the ultrasound, were approximately 67% for the popliteal vein and 95–100% for the femoral vein. Both simulation locations resulted in a pronounced reduction in venous outflow.

The study by Liu et al. [18] presents a simulation method in which the external pressure is applied by a thigh cuff during light reflection rheography (LRR) measurement. Instead of compressing a specific vein, the method evenly compresses all vessels under the cuff, including superficial veins and arteries as well as deep veins. The cuff pressures of 100 mmHg and 150 mmHg were used to simulate slight and severe DVT, respectively. Significant changes in LRR parameters were observed. Such pressure levels may approach or exceed diastolic blood pressure [19], potentially affecting arterial inflow. Liu et al. [18] did not report the effect of the pressure levels on the veins, leaving the stenosis level unclear.

Another recent study by Eitminavičius et al. [20] combines the two DVT simulation methods described above, integrating an ultrasound transducer into a compression actuator controlled by inflating an air bladder. The method provides accurate pressure control and direct visualization of the target vein. While it has some similarities to the cuff-based simulation, the pressure application is done locally from the posterior side of the leg, opposite to the transducer. Three levels of femoral vein stenosis (30%, 70%, and 100%) were selected to simulate DVT. The pressures required to achieve these levels were determined by measuring the vein's cross-sectional area under compression in the seated position using B-mode ultrasonography. Statistically significant differences in the LRR and VOP parameters were observed across the stenosis levels, with more pronounced changes during the VOP measurement.

Although these studies demonstrate the feasibility of external pressure-induced DVT simulation, the proposed methods have not been systematically compared. Furthermore, ultrasound-based approaches require relatively complex instrumentation, which may limit their applicability in early-stage diagnostic tool development. A simpler cuff-based setup could offer a more accessible alternative, provided that it achieves comparable simulation

conditions. Therefore, the aim of this study was to systematically evaluate and compare manual compression-based and cuff-based external pressure-induced DVT simulation methods.

2 Materials and methods

2.1 Study subjects

The study was evaluated by the local ethical review board of the Wellbeing Services County of Pirkanmaa and approved by the national competent authority of Finland, the Fimea (Finnish Medicines Agency). The subjects were informed about the study both orally and in written form. Before the measurements, the participants provided written informed consent.

The data were collected in a clinical study conducted at the laboratory for Health and Assistive Technology at Tampere University. VOP data were recorded from twenty healthy volunteers. All participants were over 18 years old. Diagnosed DVT in the lower limbs was considered an exclusion criterion for the study. Additionally, none of the volunteers had any other diagnosed cardiovascular diseases. The characteristics of the study population are summarized in Table 1.

Table 1 Study population characteristics.

Parameter	Median (25th percentile–75th percentile)
Number of subjects	20
Male/Female	12/8
Age (years)	24 (23–33)
Height (cm)	176 (166–183)
Weight (kg)	70 (64–84)
Systolic blood pressure (mmHg)	120 (114–127)
Diastolic blood pressure (mmHg)	65 (59–72)
Left thigh circumference (cm)	52.6 (49.9–54.9)
Right thigh circumference (cm)	52.9 (50.3–55.5)
Left calf circumference (cm)	37.3 (36.5–38.4)
Right calf circumference (cm)	36.9 (36.1–38.2)

2.2 Venous occlusion plethysmography measurement

The VOP signals were collected using the commercially available VasoScreen 1000-4000 system (medis Medizinische Messtechnik GmbH, Germany). The system is intended for arterial and venous diagnostics, including proximally located DVT. VasoScreen 1000 measures electrical impedance plethysmography (IPG) from both calves, while VasoScreen 4000 conducts temporal venous occlusion by pressurizing the thigh cuffs. The measurement setup is shown in more detail in Figure 1.

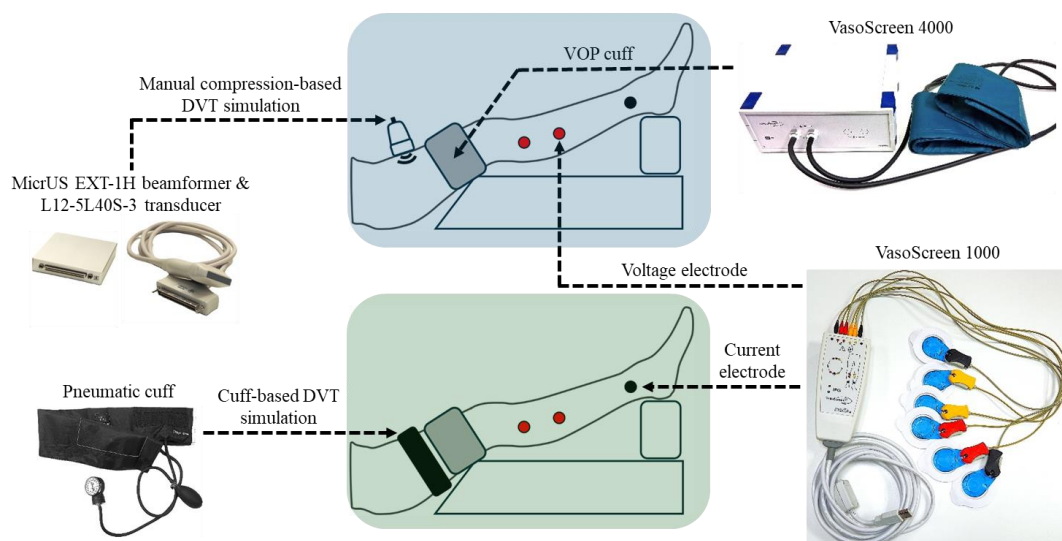


Fig. 1 Measurement setup for VOP measurement and DVT simulation. The VasoScreen 1000 measures IPG from the calf, while the VasoScreen 4000 produces temporal occlusion of the thigh veins. Manual compression-based DVT simulation was performed using an ultrasound beamformer with a transducer and cuff-based DVT simulation using a pneumatic cuff.

The VOP test was performed according to the manufacturer's instructions. During the VOP measurement, the subject was positioned in the supine position with slightly elevated legs. Correct leg positioning is crucial for the measurement, and this was ensured by the accessory pillow with a height of approximately 35 cm. The cuffs were carefully placed around the thigh, right above the knee. The measuring electrodes were attached to the skin surface on both sides of the thickest part of the calf, with an approximate distance of 10 cm between them. The excitation current electrodes were placed on both ankles. VasoScreen 1000 injects a sinusoidal excitation current (1.5 mA RMS and 86 kHz) from one leg to another and measures the voltage drop bilaterally using two pairs of measuring electrodes. Therefore, the system enables simultaneous assessment of both legs. According to the manufacturer's instruction, standard disposable ECG electrodes are intended to be used with the device. In this study, Ambu Bluesensor L wet gel electrodes (Ambu A/S, Denmark) were used.

Before the VOP measurement, the system analyses the trend, i.e., the slow baseline variations in the IPG signal. The trend is temporary and stabilizes as blood flow becomes steady. When no significant trend is present, the thigh cuffs are inflated to the pressure of 40 mmHg, then to 60 mmHg, and finally to 80 mmHg. Each pressure level is applied until the blood volume curve achieves a plateau or maximum time is reached. After the final pressure level, the system rapidly deflates the thigh cuffs, causing venous outflow. After the deflation, the signal is still recorded for 45 seconds.

The system calculates six parameters from the VOP curve: 1) arterial inflow; 2) venous capacity; 3) venous outflow within two seconds; 4) outflow volume within three seconds; 5) outflow volume within five seconds; and 6) outflow time constant. The parameters are described in more detail in Table 2.

The system utilizes the venous capacity and venous outflow within two seconds for diagnosing DVT. In the graphical user interface, venous outflow is plotted as a function of venous capacity with predefined boundaries for classifying samples as normal or pathological. Other parameters may also be used by healthcare professionals to support the diagnosis, but thresholds for these parameters are not provided.

Table 2 Venous occlusion plethysmography parameters recorded by VasoScreen 1000, their symbols (in this study), units, and definitions.

Parameter	Symbol	Unit	Definition
Arterial inflow	AI	%/min	The steepest rise during the occlusion.
Venous capacity	VC	%	Maximum change in venous blood volume during the measurement.
Venous outflow (2s)	VO_{2s}	%/min	The rate of the blood during the first two seconds after the deflation.
Outflow volume (3s)	OV_{3s}	%	The relative change in blood volume during the first three seconds after the deflation.
Outflow volume (5s)	OV_{5s}	%	The relative change in blood volume during the first five seconds after the deflation.
Outflow time constant	τ	s	The time constant of fitted exponential to the decline after the deflation.

2.3 Deep vein thrombosis simulation

In the present study, DVT was simulated using two different approaches: 1) manual occluding the femoral vein by an ultrasound transducer, and 2) by compressing the thigh using another cuff. DVT simulation methods are illustrated in Figure 1.

In the manual compression-based DVT simulation with ultrasound imaging, the femoral vein was occluded by applying targeted external pressure using an ultrasound transducer. The ultrasound system used in the study was the MicrUS EXT-1H beamformer with L12-5L40S-3 linear transducer (Teleded UAB, Lithuania). B-mode ultrasonography was used to locate the femoral vein at the mid-thigh, and pressure was increased until the venous lumen was completely occluded. Simulation only with full stenosis was implemented because inducing a partial stenosis was found challenging for two reasons: manual (by hand) control of the ultrasound transducer was imprecise to induce a specific stenosis level, and venous pressure was low in the supine position, often making the femoral vein nearly invisible. Additionally, the effect of manual compression-based simulation on the shape of the VOP curve was relatively small in initial tests, even though the femoral vein was fully occluded.

In the cuff-based DVT simulation, another cuff was placed around the thigh just above the VOP cuff. The width of this cuff was approximately 11 cm. Three different simulation pressures were selected based on the initial tests to simulate partial, moderate, and full occlusion of the vein. The pressure levels were: 25 mmHg, 40 mmHg, and 60 mmHg, respectively. The degree of stenosis induced by each selected pressure was estimated by measuring the cross-sectional area of the femoral vein using B-mode ultrasonography. This was done in a sitting position because the accurate imaging of the veins is difficult in the supine position due to the low venous pressure. Thus, sitting was considered by the authors to be the best position for estimating the stenosis level under simulation.

pressure, as the hydrostatic pressure in this position may correspond to the kinematic pressure caused by venous outflow during VOP cuff deflation. A cuff similar to the simulation cuff was used to assess pressure-induced stenosis, but a small opening was made in the middle for the ultrasound transducer.

2.4 Study protocol

The protocol of the study consists of five consecutive VOP measurements, as illustrated in Figure 2. The first measurement was a standard VOP measurement without simulation, after which four measurements with DVT simulation were conducted. In each condition, both legs were measured simultaneously. The first simulated measurement was performed using the manual compression-based DVT simulation, whereas the three subsequent measurements were done with the cuff-based DVT simulation at decreasing pressure levels: 60 mmHg, 40 mmHg, and 25 mmHg. Before each measurement, the IPG baseline was allowed to stabilize. The descending order was selected because venous outflow following simulation cuff pressure release is faster than venous pooling in response to pressure increase. This shortened the overall protocol duration because starting from the highest simulation pressure avoided slow venous pooling between simulation pressure changes. However, the break was always at least three minutes, which is enough to avoid too frequent measurements according to the manufacturer.

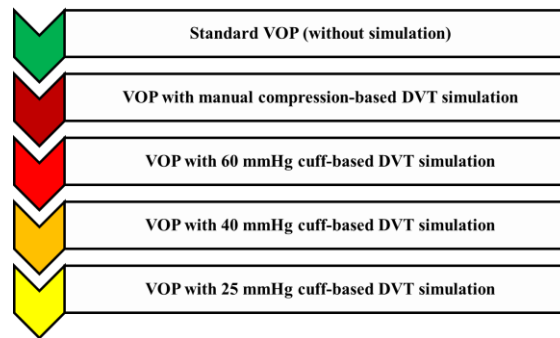


Fig. 2 The protocol of the study. The first standard VOP measurement was conducted, after which the test was repeated four times using different DVT simulations. The break between the tests was at least three minutes. Standard VOP and DVT simulations are color-coded consistently throughout the paper.

2.5 Statistical analysis

The Shapiro-Wilk test was utilized to assess the data normality before evaluating different DVT simulation methods. Since several VOP parameters were not normally distributed, the results were presented as medians and percentiles, and also non-parametric statistical tests were used. The Friedman test was used to evaluate differences between different conditions. When a statistically significant difference was observed, pairwise post hoc tests were further performed using MATLAB's *multcompare* function (Mathworks Inc., USA) with the Dunn-Šidák correction for multiple comparisons. A p -value less than 0.05 was considered statistically significant in this study.

To evaluate the change induced by each simulation relative to standard VOP measurement, the relative changes were calculated for each subject. The relative changes were summarized using boxplots for each parameter separately. Finally, venous outflow (2s) and venous capacity were visualized in a scatter plot with classification boundaries, and the sensitivity for detecting simulated DVT and the test specificity were calculated.

3 Results

3.1 Induced stenosis levels

The stenosis level caused by manual compression-based DVT simulation was monitored during the VOP measurement using ultrasound B-mode. Although obtaining a good image quality in real-time was challenging, full occlusion was achieved relatively reliably. The aim was to maintain sufficiently high external pressure to fully occlude the femoral vein throughout the entire VOP measurement. Especially during VOP cuff release, the vein lumen at the site of the ultrasound transducer tends to open due to the rushing blood. The pressure applied with the ultrasound transducer was kept sufficiently high to prevent this lumen opening. Therefore, the stenosis level is estimated to be approximately 100% during the manual compression-based DVT simulation.

Measured stenosis levels for different cuff-based DVT simulation pressures in the sitting position were (the values are presented as median and interquartile range): 44% (38–50%) at 25 mmHg, 62% (60–68%) at 40 mmHg, and 86% (81–88%) at 60 mmHg. Stenosis could not be measured in three subjects due to poor ultrasound B-mode image quality. According to the Friedman test, the differences between stenosis levels were statistically significant. Post hoc pairwise comparisons revealed statistically significant differences between all stenosis level pairs.

3.2 Time domain signals

Averaged VOP signals across subjects during the standard measurement, manual compression-based DVT simulation, and different pressures of cuff-based DVT simulation are shown in Figure 3. Notable changes in signal morphology were observed during each simulation method. In particular, venous capacity decreased, accompanied by reduced venous outflow.

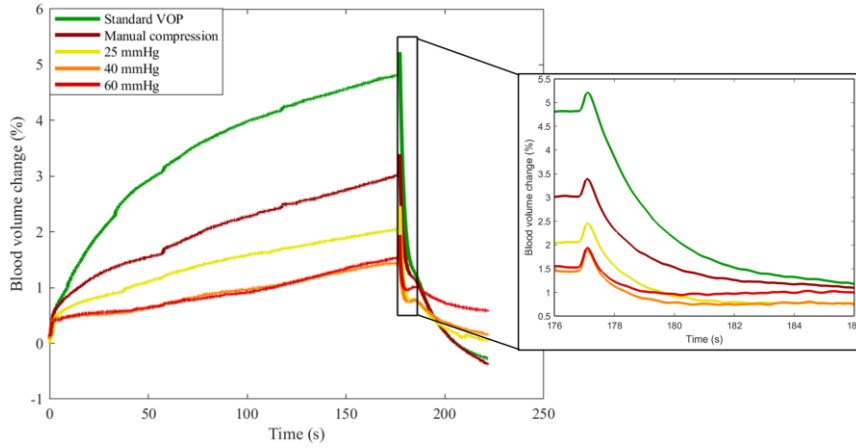


Fig. 3 Averaged VOP signals for standard condition, manual compression-based DVT simulation, and the different pressures of cuff-based DVT simulation.

The greatest reduction was observed at the highest simulation cuff pressures (40 mmHg and 60 mmHg). The effect of these DVT simulations was relatively similar. The manual compression-based DVT simulation caused the smallest effect, although the femoral vein was fully occluded. The reduction in venous capacity at the pressure of 25 mmHg is intermediate between the manual compression and the two highest simulation pressures.

3.3 VOP parameter analysis

The medians and the 25th and 75th percentiles of all six VOP parameters obtained using the VasoScreen 1000-4000 system are presented in Table 3. Each DVT simulation reduced the median of all VOP parameters except for the outflow time constant, which was increased.

Table 3 VOP parameters for standard condition and different DVT simulations. The values are presented as Median (25th percentile–75th percentile).

Parameter	Standard VOP	Manual compression	25 mmHg	40 mmHg	60 mmHg
AI (%/min)	4.1 (3.6–5.2)	2.1 (0.9–3.1)	1.0 (0.4–1.65)	0.2 (0–0.6)	0.2 (0–0.55)
VC (%)	5.00 (4.05–5.98)	3.35 (2.35–4.52)	1.95 (1.14–2.60)	1.27 (0.92–1.93)	1.06 (0.83–1.47)
VO_{2s} (%/min)	62 (43–87)	36 (17–57)	28 (16–42)	20 (9–30)	16 (8–23)
OV_{3s} (%)	3.51 (2.50–4.20)	1.69 (0.83–2.69)	1.30 (0.65–1.80)	0.78 (0.33–1.13)	0.54 (0.31–0.78)
OV_{5s} (%)	3.71 (2.58–4.47)	1.86 (0.82–2.91)	1.32 (0.59–1.90)	0.77 (0.35–1.16)	0.54 (0.27–0.76)
τ (s)	4.4 (3.6–4.9)	6.7 (5.4–9.5)	4.9 (4.1–6.1)	5.8 (4.7–8.0)	8.7 (5.4–11.6)

The Friedman test revealed significant differences between different conditions for all parameters at the significance level of 0.05. Therefore, the differences between the two specific conditions were further analyzed using pairwise post hoc tests using. The p -values of the post hoc comparison are presented in Table 4. The values less than 0.05 were considered statistically significant.

Statistically significant differences were found in almost all parameters between standard and simulated conditions. Compared to standard VOP measurement, only venous capacity during the manual compression-based DVT simulation and outflow time constant during the cuff-based DVT simulation at 25 mmHg were not statistically significant. In turn, there was no statistically significant difference between the manual compression-based simulation and cuff-based simulation at 25 mmHg, except for the venous capacity and outflow time constant. As expected, based on the time-domain signals (Figure 3), no statistically significant differences were found between cuff-based simulations at 40 mmHg and 60 mmHg.

To evaluate changes in VOP parameters caused by different simulation methods, relative changes compared to the standard measurement were calculated. The relative changes are summarized in Figure 4 using boxplots.

Except for the outflow time constant, the manual compression-based simulation caused the smallest relative change in the medians of all parameters, whereas more pronounced changes were achieved using the cuff simulation. For the time constant, the manual compression-based simulation produced the second largest increase immediately after the cuff-based simulation at 60 mmHg. For the cuff-based simulation, the median parameter changes increased with increasing simulation pressure.

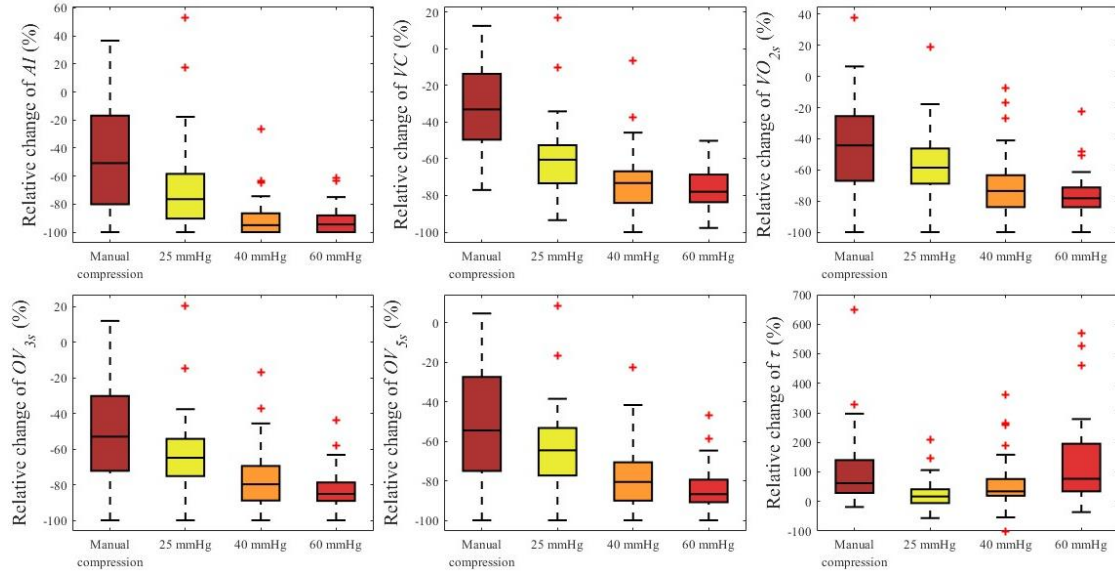


Fig. 4 Relative changes of VOP parameters for different simulations compared to the standard measurement, with the colored box showing the interquartile range and the whiskers the total range. Values deviating from the median more than 1.5 times the interquartile range have been marked with a red sign.

Table 4 p -values of the Dunn-Sidak corrected pairwise post hoc comparison for all parameters. The values less than 0.05 are considered statistically significant.

	Manual compression	25 mmHg	40 mmHg	60 mmHg
Standard VOP	AI : 0.003	AI : < 0.001	AI : < 0.001	AI : < 0.001
	VC : 0.057	VC : < 0.001	VC : < 0.001	VC : < 0.001
	VO_{2s} : 0.002	VO_{2s} : < 0.001	VO_{2s} : < 0.001	VO_{2s} : < 0.001
	OV_{3s} : < 0.001	OV_{3s} : < 0.001	OV_{3s} : < 0.001	OV_{3s} : < 0.001
	OV_{5s} : 0.002	OV_{5s} : < 0.001	OV_{5s} : < 0.001	OV_{5s} : < 0.001
	τ : < 0.001	τ : 0.184	τ : < 0.001	τ : < 0.001
Manual compression		AI : 0.439	AI : < 0.001	AI : < 0.001
		VC : 0.029	VC : < 0.001	VC : < 0.001
		VO_{2s} : 0.556	VO_{2s} : < 0.001	VO_{2s} : < 0.001
		OV_{3s} : 0.785	OV_{3s} : < 0.001	OV_{3s} : < 0.001
		OV_{5s} : 0.788	OV_{5s} : < 0.001	OV_{5s} : < 0.001
		τ : 0.003	τ : 0.984	τ : 0.956
25 mmHg			AI : 0.009	AI : 0.006
			VC : 0.015	VC : 0.002
			VO_{2s} : 0.025	VO_{2s} : < 0.001
			OV_{3s} : 0.014	OV_{3s} : < 0.001
			OV_{5s} : 0.008	OV_{5s} : < 0.001
40 mmHg			τ : 0.076	τ : < 0.001
				AI : 1.000
				VC : 1.000
				VO_{2s} : 0.827
				OV_{3s} : 0.831
				OV_{5s} : 0.834
				τ : 0.327

3.4 Classification of simulated DVT

Finally, the VOP measurements were classified using the thresholds provided by the VasoScreen 1000-4000 system. The system plots venous outflow within 2 seconds as a function of venous capacity and provides classification boundaries for the scatter plot. Figure 5 shows the VOP data collected in this study with the various DVT simulation methods, plotted with the classification boundaries.

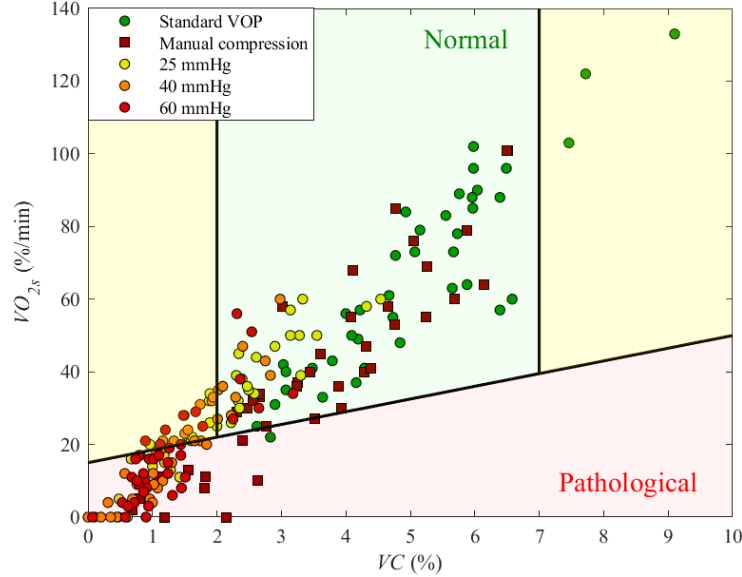


Fig. 5 Venous outflow within two seconds as a function of venous capacity. The green and red areas represent normal and pathological test results, respectively. Yellow areas illustrate the cases where the venous capacity is either very low or very high, while the venous outflow is normal.

In Figure 5, the green area represents a normal test result, while the red area - pathological result. The interpretation of the yellow areas is more challenging, as they indicate abnormally low or high venous capacity values, while the venous outflow is normal. Table 5 summarizes how the VOP tests of the study fell into different areas.

Table 5 Summary of how the measurement fell into different classification areas. Both legs were investigated and included in the analysis.

Condition	Green Area	Lower Yellow Area	Upper Yellow Area	Red Area
Standard VOP	36	0	3	1
Manual compression	28	0	0	12
25 mmHg	20	7	0	13
40 mmHg	9	9	0	22
60 mmHg	6	6	0	28

Very high venous capacity often means a healthy measurement rather than a pathological one. Additionally, very low venous capacity (less than 2%) can usually be seen in DVT patients [21]. Therefore, the left-side yellow area was considered pathological, and the right side was considered normal in this study. Using these interpretations as binary classification rules, the obtained specificity of the test was 97.5% for all simulation methods, and sensitivity 30.0% for manual compression-based DVT simulation, 50.0% for cuff-based DVT simulation at 25 mmHg, 77.5% for cuff-based DVT simulation at 40 mmHg, 85.0% for cuff-based DVT simulation at 60 mmHg, and 60.6% for all DVT simulations.

5 Discussion

Developing non-invasive, operator-independent diagnostic tools for the continuous monitoring of DVT is critical for improving early detection and reducing the risk of pulmonary embolism. However, the rigorous regulatory requirements and challenges associated with recruiting fragile patients for pilot-phase studies necessitate the development of reliable methods to simulate DVT-like hemodynamic changes in healthy volunteers. This study

systematically compared two such simulation methods, manual ultrasound transducer compression and thigh cuff compression to assess their effectiveness in mimicking the venous obstruction characteristic of DVT.

Excluding the time constant, the largest medians of the relative changes (Figure 4) were observed at higher cuff pressures (40 and 60 mmHg), whereas the cuff-based DVT simulation at 25 mmHg and the manual compression-based DVT simulation produced smaller changes. The same trend can also be visually observed in the time-domain signals (Figure 3). Although each simulation pressure caused only partial stenosis (44%, 62%, and 86%, respectively), it is expected that sufficiently high cuff pressure can produce a larger change compared to the manual compression-based simulation, because the cuff-based simulation not only occludes a specific vein but also compresses all the veins under the cuff, including the superficial, perforating, and deep veins. For the outflow time constant, the manual compression-based simulation, surprisingly, caused a large change on average. This is likely because the manual compression-based DVT simulation primarily slows down the venous outflow dynamics rather than reducing the maximum blood volume change. Other outflow parameters (VO_{2s} , OV_{3s} , and OV_{5s}) also depend on the maximum change, while the time constant is the temporal parameter, reflecting how quickly the system responds.

There were no statistically significant differences found between the 40 mmHg and 60 mmHg simulation pressures, indicating their effects on the VOP signal are very similar. This may occur because the pressure of 40 mmHg already occludes the veins effectively in the supine position [22], and increasing the pressure to 60 mmHg no longer produces a significant additional change. However, in this study, stenosis levels of 62% at 40 mmHg and 86% at 60 mmHg, with a statistically significant difference ($p < 0.05$), were measured. Therefore, estimating stenosis in the sitting position may be inaccurate, as the hydrostatic pressure in the sitting position differs from the kinematic pressure caused by the venous outflow after VOP cuff deflation.

Comparing the results of this study with literature on actual DVT patients remains challenging because the results vary substantially due to the large variation in the VOP methods used across studies. For example, the measured maximum volume change during the VOP test depends on the occlusion time, and this maximum change further affects the observed venous outflow [23]. Comparing parameter values is also difficult because blood volume changes have previously been reported using various scaling factors. Nevertheless, the results of this study align with the literature because actual DVT is known to reduce venous capacity and venous outflow [14, 15, 24]. Furthermore, the outflow time constant is naturally higher in DVT patients, indicating slower venous outflow. A large meta-analysis by Locker et al. [11] suggests a specificity of 90% and a sensitivity of 88% for proximal DVT using the VOP test. However, comparing these metrics with the values obtained in this study is problematic because the performance depends not only on the parameter values but also on the classification thresholds used. According to the knowledge of the authors, the performance of the VasoScreen 1000-4000 system and its classification thresholds in DVT patients has not been reported in scientific literature.

The study also revealed several differences between simulation and actual pathology. Although the performance of the VOP method for detecting DVT varies widely across studies, it has been reported that a fully occlusive proximal DVT causes a noticeable change in the VOP signal morphology [15, 25]. However, the median change caused by the fully occlusive manual compression-based simulation is relatively small. This may result from several factors. DVT not only occludes the vein but also causes thickening and stiffening of the venous wall [26]. This can further reduce venous compliance and the capacity of veins to store blood. Thus, the hemodynamic changes caused by actual DVT may be greater than those caused by the manual compression-based simulation. On the other hand, chronic DVT promotes collateral vein formation, providing alternative pathways for venous outflow and reducing observable changes [14, 27]. In any case, the hemodynamic effect of actual DVT is more complex than that of the manual compression-based simulation, which only temporarily occludes the specific vein. It is also noteworthy that the effect of manual compression-based simulation on VOP parameters varied greatly between subjects. This may indicate that manual control of the transducer was inherently unreliable. Several limitations should be noted. The number of subjects was relatively small, with only twenty participants (8 females). By measuring both legs, forty VOP measurements were obtained. In addition, the study population was relatively homogeneous, consisting mainly of young adult volunteers without any underlying conditions. Young individuals typically have large venous compliance, which decreases substantially with age [28]. Other underlying conditions besides DVT can also affect venous hemodynamics, producing false-positive results. For example, a tumor may compress a vein and disturb normal venous flow, or arterial insufficiency may lead to slower venous filling in response to VOP cuff inflation [15]. Therefore, to produce more generalizable results, the different simulation methods should be tested on a larger study population consisting of subjects of various ages and health conditions. The stenosis caused by different cuff pressures was estimated by measuring the cross-sectional area of the femoral vein. Thus, it remains unclear how the pressure affected the superficial veins, as the ultrasound setup did not allow measurement of the full cross-section of the thigh. It may be that superficial veins collapse slightly earlier because they are located closer to the surface than deep veins, which are surrounded by large muscles and other tissues. However, we assume that the stenosis in all veins was relatively uniform in the steady-state condition, as the simulation cuff applies the pressure uniformly around the thigh. In both DVT simulation methods (manual compression-based and cuff-based simulations), pressure also affected the arteries,

particularly the femoral artery. However, the applied pressure was low compared to arterial pressure, and thus its effect was assumed to be negligible. Finally, it should be emphasized that the hemodynamic changes caused by simulation methods presented in this study depend on the size of the cuff or the ultrasound transducer. A longer occlusion induces vein lumen reduction over a greater distance and increases venous flow resistance [29], which needs to be taken into account when performing DVT simulations with this method.

In conclusion, both manual compression-based and cuff-based DVT simulation methods are feasible for simulating DVT-like hemodynamic changes, though they offer different advantages. The cuff-based approach is simple, inexpensive, and produces pronounced changes with precise pressure control, making it well suited for early-stage development of diagnostic tools. In contrast, manual compression-based simulation allows for the assessment of stenosis levels but is technically demanding and offers less reliable pressure control. Future refinements could involve integrating an ultrasound transducer within a simulation cuff, as previously explored using a compression actuator [20], to combine the benefits of direct visualization and accurate pressure control when more advanced simulations are required.

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Declarations

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Conflict of interest. The authors declare that they have no conflict of interest related to this study. Devices for data collection, VasoScreen 1000-4000 (medis Medizinische Messtechnik GmbH, Germany) and MicrUS (Telemed UAB, Lithuania), were provided by ThrombUS+ partners for the purposes of the project. The devices themselves were not the subject of the study, and the companies had no role in study design and manuscript preparation.

Ethics approval and consent to participate. The study was approved by the local ethical review board of the Wellbeing Services County of Pirkanmaa and by the national competent authority of Finland, the Fimea (Finnish Medicines Agency). All participants were informed of the study orally and in written form and provided written informed consent.

Data availability. The data that support the findings of this study cannot be made publicly available or shared due to ethical and privacy restrictions related to personal information.

Author contributions. S.M. contributed to the study design, data collection, data analysis, interpretation of results, and manuscript writing and revision. N.K. contributed to the study design, data collection, and manuscript revision. R.E. interpreted the results and revised the manuscript. R.A. contributed to the study design and revised the manuscript. A.K. contributed to the study design, data collection, and manuscript revision. R.J., A.R., V.M., and E.K. interpreted the results and revised the manuscript. A.V. supervised the study, contributed to the study design, interpreted the results, and revised the manuscript.

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