Digital Photoplethysmography in the Diagnosis of Deep Vein Thrombosis in Thai Patients

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Background: *In Western countries, an incidence of deep vein thrombosis (DVT) in the lower limb is roughly 2.5-5%. If left untreated, this conditon carrys a significant mortality rate due to pulmonary embolism (PE) as well as an increase in morbidity due to chronic venous insufficiency and venous ulceration., In Thailand, the rate of incidence has not, as of yet been established. Though, DVT is not an uncommon disease . A known gold standard test, for DVT is duplex ultrasonography, which with its sensitivity and specificity is more than 95% accurate. Negative aspects of this test are expense, technically demands, time-consuming and not widely available. As an alternative, the digital photoplethysmography (D-PPG) can be a simple, non-invasive, reliable and non-operator device that can effectively test screen in the diagnosis of DVT.*
Objective: *To determine the role of digital photoplethysmography (D-PPG) and the optimum cut off-point of venous refilling time (RT) and venous pumping (VP) in the diagnosis of DVT when compared with duplex ultrasonography.*
Material and Method: *Prospective study of 80 patients (127 swelling limbs) where clinical manifestations of DVT was suspected in lower limbs. Each patient was assessed by D-PPG and duplex ultrasonography.*
Results*: In 80 patients, 127 limbs were found to have had swelling of the lower limbs and 50 limbs had DVT as demonstrated by duplex ultrasonography. Using RT with a range of 19-21 second intervals as the optimal cut-off point, D-PPG achieved a sensitivity rate of 94%, a negative-predictive value of 92%, a specificity of 58%, and a positive-predictive value of 52%.*
Conclusion*: These results were validated by using D-PPG as a useful screening device in the diagnosis of patients with swelling limbs who were clinically suspected of contracting DVT of the lower limb. Patients who tested positive (for DVT) required further confirmation by duplex ultrasonography, where as a negative result (via RT >21s) excluded DVT.*

Keywords: *Deep vein thrombosis, Digital photoplethysmography, sensitivity and specificity*

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Deep vein thrombosis (DVT) is a common medical condition with incidences of roughly 2.5-5% among the general population of western countries[1]. If we left untreated, DVT can lead to pulmonary embolism (PE), chronic venous insufficiency and venous ulceration. Within the vascular surgery division at Siriraj Hospital, roughly 2,500 -3,000 patients annually have visited our clinic suffering from swelling limbs. In each case duplex ultrasonography was required to confirm DVT. Roughly two-third of the patients did not have DVT. Only 33% of swelling leg, patients could be demonstrated DVT in proximal veins by duplex scan[2]. Duplex ultrasonography is the gold standard in the diagnosis of DVT and with its sensitivity and specificity rates it records more than 95%[3] accuracy. Though, there are some negative aspects to this method such as, time consumption, being operator dependent, back log in patient queues, exorbitant costs which ultimately limits case investigations.

Photoplethysmography (PPG) is a non-invasive optical technique which has been widely used as a simple clinical method for assessing venous function. Digital photoplethysmography (D-PPG) is yet a further development with the use of analogue light-reflection rheography (LRR)[4], which is based on the principle of PPG. PPG uses light absorbance from hemoglobin as a reflection of blood volume in the venous and capillary networks within the skin. This process estimates the degree of venous stasis. PPG also uses a transducer that emits an infrared light from a diode, into the dermis. The backscattered light is measured by an adjacent photo-detector, and net

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absorption is displayed as a line tracing. Absorption of light in hemoglobin is high when skin venous and capillary blood is increased during sitting or standing; conversely, it is decreased during exertion when venous blood is expelled from the limb by the action of calf muscles. With this technique, the venous refilling time measurement is standardized, and by measuring the extent of blood displacement from the calf, assessment of the calf pump efficacy becomes possible.

Previous studies are available regarding the use of D-PPG in the assessment of DVT, though no study, as of yet has been conducted within the Thai population[5-7]. D-PPG detects changes in blood content of the dermis by measuring infra-red light reflected from the dermal microcirculation of the leg. The photoplethysmographic refilling time has recorded a good correlation with the venous pressure refilling time (RT) (or, direct intravenous pressure measurement)[8]. In a normal subject, activation of the calf muscle pump (dorsiflexion of the foot) will result in a reduction of venous pressure and dermal blood volume. On the D-PPG, these physiological changes translate as a decrease in light absorption and light reflection. The efficacy of the calf pump depends on the percentage of displacement of initial blood volume. This efficacy is reflected on the D-PPG. Similarly, the displacement of initial blood volume is reflected on the D-PPG by the percentage change of light absorption and light reflection. Displacement of blood will be reduced or restricted in patients with venous valvular or venous obstructive disease as in DVT. The light absorption and reflection signals return to baseline upon completion of the charted course as venous refilling occurred. Elapse time for venous filling after completion in a normal subject depends entirely on the arterial inflow. Normal venous refilling time has been reported to range from 18-40 seconds. However, the refilling time of the dermal microcirculation can be reduced by direct invasive venous reflux procedure. On the other hand, in DVT with obstruction to deep veins, the rate at which blood exits form the calf and skin slows down and consequently venous refilling time become shorter.

The aim of this study was to determine the role of D-PPG in the diagnosis of DVT in Thai patients by comparison to the duplex ultrasound (gold standard) and to establish a proper cut-off point for refilling time (RT) in the diagnosis of DVT.

Material and Method

This was a prospective study of 80 patients between November 2009 and October 2011 at Siriraj Hospital, Bangkok, Thailand. Patient conditions were (127) swelling legs and suspected DVT. These patients were investigated for proving DVT by using D-PPG either before or within 24 hours after duplex ultrasonography (9 MHz linear array transducer). Duplex ultrasonography is regarded as the gold standard in this study for the diagnosis of DVT.

The D-PPG device, which was used in this study (Rheo Dopplex II PPG Huntleigh Diagnostic Ltd., Cardiff, UK) contained two light-emitting diodes (LED) and two adjacent photo-detectors. This allowed for continuous recording of relative blood volume in the dermal microcirculation as it would result from venous emptying and refilling. The process involves an infra-red light with a transmitting wavelength of 950 nm being beamed into the dermal microcirculation. The light is then absorbed by the red blood cells and is reflected back to the photo-detector. The variance in light activity is then converted into a digital signal and recorded for analysis.

For the D-PPG examination, the patient was examined in a sitting position with the foot of the affected leg resting flat on the floor and the knee flexed at an angle of roughly 110 degrees. The sensor was attached to an area of skin approximately 10 cm superior to the medial malleolus with double-sided adhesive tape. The D-PPG unit was then activated. Calibration of the D-PPG unit typically took between 30 s to 1 min. The patient was then instructed to dorsiflex the foot in succession for 10 repetitions to an audible metronome. This was followed by resting the foot completely for 45s. This period would be the venous refilling phase. After completing the exercise the patient was also requested to refrain from talking, deep breathing or moving, as these may distort the venous refilling time. Upon completion of the test, venous refilling time (RT) and venous pump (VP) (efficacy of calf pump as represented by the amplitude of D-PPG curve) were automatically displayed on the LCD. A printout of results with D-PPG curve was produced (Fig. 1 and 2).

Duplex ultrasound was performed as follows: Femoral veins and popliteal veins were assessed with the patient in a supine position. The transducer probe of 9 MHz was used for assessing the veins and was then placed on the entirety of selected veins. This demonstrated echogenicity, color filling in the veins and compressibility. Duplex ultrasonographic findings were as follows: Hypo and hyper echogenicity, color filling defect in the veins and loss of their compressibility usually indicates thrombus in the veins. Pressure was applied using the transducer probe over

the vein to check their compressibility and flow augmentation. Inspection of the vein during direct compression was also performed. The presence of DVT was indicated when the vein failed to be compressed or there was absence of color in the vein lumen even with flow augmentation. Additional data was recorded for each patient including age, and BMI. Ethics Consideration: 551/2552(EC2)

Statistical analysis

A comparison between the new test (D-PPG) and the gold standard (duplex ultrasonography) was performed. Sensitivity, specificity, positive and negative predictive values were determined. Receiver operating characteristic (ROC) curves were constructed for each parameter. The area under each curve was calculated to reveal their discriminatory power for the new test. Statistical analysis was performed using STATA/SE 10.0

Results

A total of 127 swelling legs from 80 patients with suspected DVT were accessed in this study. The study sample of 50 female and 30 male had a mean age of 61 and 57 years respectively.

The demographic profile of the study sample was demonstrated in Table 1. 15 legs from without DVT group also found to have varicose veins and reflux.

The RT and VP were the parameters of D-PPG used to compare with duplex ultrasonography, which is the gold standard method. Comparison of RT and VP values between patients without and with DVT were illustrated in Fig. 3 and 4 respectively. Patients with DVT had a statistically significant shorter RT than those patients without DVT. VP value did not show statistical difference between two groups.

The discriminatory power (area under the curve) of RT was 76%. The optimal cut-off point for each parameter (RT and VP) obtained should achieve maximum true positive rate (sensitivity) to compromising specificity (i.e. higher false-positive rate). RT of 19s - 21s were the optimal cut-off points obtained from the ROC curve based on the above criteria. The sensitivity, specificity, positive-predictive value, negative-predictive value, likelihood ratio for positive and negative test and of different cut-off points for RT were illustrated in Table 2

By using RT of equal to or less than 19s as the optimal cut-off point in indicating the presence of DVT, a sensitivity of 94% (95% confidence interval), negative-predictive value of 92%, specificity of 58% and positive-predictive value of 52% were achieved. The same results were shown in RT of less than 20s and 21s. In VP we could not conclude the optimal cut-off point due to the variation in the results. The different cut-off point for VP was illustrated in Table 3

Discussion

DVT is a widespread disease with an incidence of 2.5% to 5% in the general population of western countries[1]. Clinical diagnosis of patients with suspected DVT is unreliable. Therefore, clinical diagnosis alone of suspected DVT may result in unnecessary hospitalization of patients and inappropriate anticoagulation therapy with potentially dangerous consequences.

The accurate diagnosis of DVT typically needs investigation. Duplex ultrasonography is the gold standard test with its sensitivity and specificity at more than 95%[5].Though, this test still has some limitations, as mentioned.

Digital photoplethysmography (D-PPG) can be an accurate and efficient screening test for the diagnosis of DVT[6]. This test requires a short implement time and does not require an expert technician. PPG uses light absorbance from hemoglobin as a reflection of blood volume in the venous and capillary networks in the skin to estimate the degree of venous stasis. Parameters from PPG, which can be reflected venous function are VRT and VP. VRT is defined as the time, in seconds required for skin microcirculation to refill after a series of calf muscle contractions which squeezes the veins and propels blood up and out the legs. Lower VRT (<25s) is indicative of venous insufficiency. Venous pump (VP) defines efficacy of calf pump as represented by the amplitude of D-PPG. PPG is a further development of light-reflection rheography (LRR), though with several advantage over LRR. D-PPG can be calibrated and allows for quantitative evaluation of blood displacement by compensating for different cutaneous optical densities. These variances in densities are a result of skin color, skin thickness and initial local blood volume. In addition, numerical results obtained with the D-PPG device are readily displayed on the LCD screen. This therefore, significantly reduces bias introduced in LRR due to subjective interpretation for positive or negative results based on the shape of the curve of a parameter form the graph. A limitation of the use of D-PPG is in the group of patients who are unable to accurately comply with the exercise program (i.e. performing ten successive foot dorsiflexions), due to

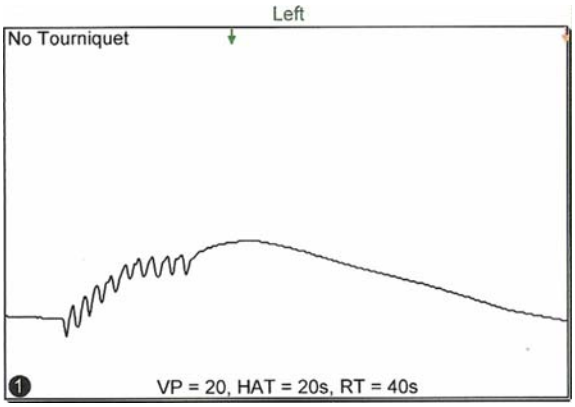

Fig. 1 D-PPG graph in normal patient.

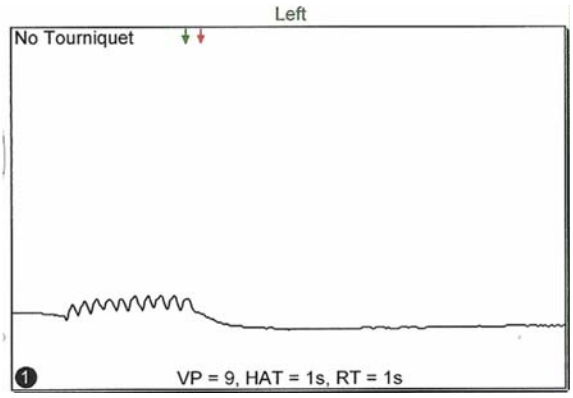

Fig. 2 D-PPG graph in DVT patient

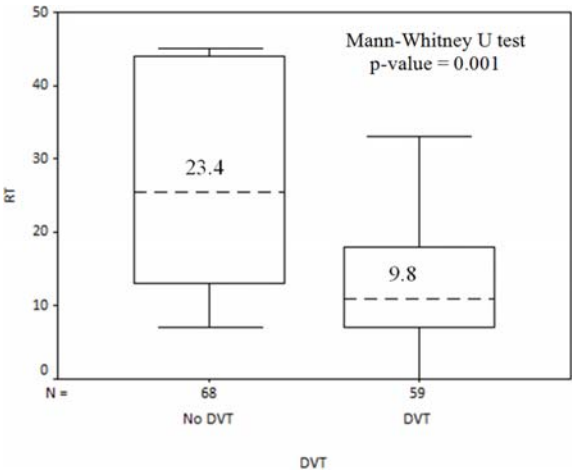

Fig. 3 Box-whisker plot of RT in patients without and with DVT. The median value is indicated by the horizontal line within the box.

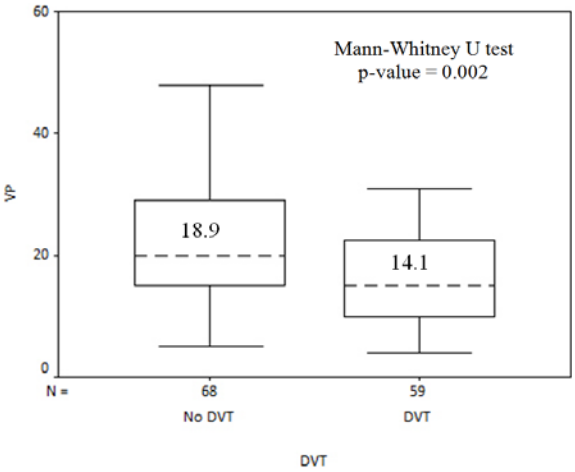

Fig. 4 Box-whisker plot of VP in patients without and with DVT. The median value is indicated by the horizontal line within the box.

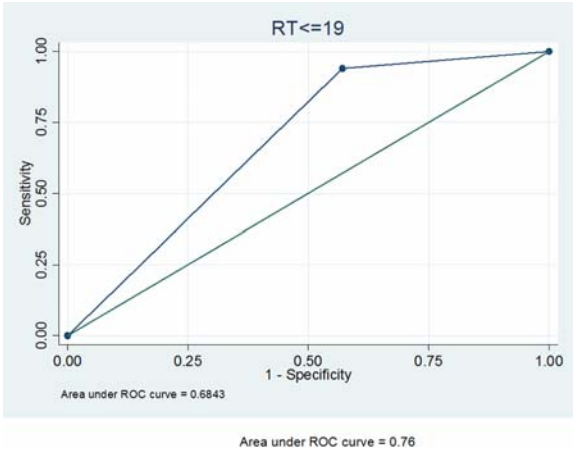

Fig. 5 ROC curve was constructed for the RT

confusion, paralysis or skin lesion in the median side of the ankle.

From previous studies using RT of less than 21s as the optimal cut- off point, D-PPG achieved a sensitivity of 100%[4,6,8], negative predictive value of 100%, specificity of 47% and positive-predictive value of 51%. By using VP less than 36s as the optimal cut-off point, a sensitivity of 100%, a negative-predictive value of 100%, a specificity of 35% and positive-predictive value of 46% were achieved. This study recorded nearly the same results as from previous studies in cut-off points of RT (19-21s).

Conclusion

These results validate the use of D-PPG as a useful screening device for the diagnosis of clinical suspected lower limb DVT (limb swelling). A positive

Table 1. The demographic characteristics of study population

Characteristics data	No DVT	DVT	*p*-value
Sex (80 patients)			0.083
Female	30	20	
Male	12	18	
Age(mean)	61	57	0.296
BMI(mean)	24.53	23.78	0.457
Limb swelling (127 legs)	77	50	<0.001
Refulx (legs)	15	0	<0.001

Table 2. Comparison of different RT cut-off points

Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	ROC area
17	86%	60%	51%	84%	1.62	0.30	0.72
18	86%	60%	51%	84%	1.62	0.30	0.72
19	94%	58%	52%	92%	1.65	0.14	0.76
20	94%	58%	52%	92%	1.65	0.14	0.76
21	94%	58%	52%	92%	1.65	0.14	0.76
22	94%	56%	51%	91%	1.57	0.15	0.75
23	94%	56%	51%	91%	1.57	0.15	0.75

Table 3. Comparison of different VP cut-off points

Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	ROC area
10	42%	78%	55%	67%	1.90	0.74	0.60
11	46%	71%	51%	67%	1.61	0.76	0.59
12	54%	69%	53%	70%	1.73	0.67	0.61
13	60%	64%	52%	71%	1.65	0.63	0.62
14	64%	62%	52%	73%	1.70	0.58	0.63
15	66%	56%	49%	72%	1.49	0.61	0.61
16	70%	55%	50%	74%	1.54	0.55	0.62
17	74%	49%	49%	75%	1.46	0.53	0.62
18	74%	43%	46%	72%	1.30	0.61	0.58
19	76%	40%	45%	72%	1.27	0.60	0.58
20	78%	35%	44%	71%	1.20	0.63	0.57

test requires further confirmation by duplex ultrasonography, where as a negative test (RT >21) can exclud DVT.

What is already known on this topic?

Deep vein thrombosis can be diagnosed with duplex ultrasonography which is the gold standard test. However, this test is expensive, technically demanding and time consuming. The digital photoplethysmo graphy (D-PPG) is a simple, non-invasive and non operator depending test which can be a useful test for screening diagnosis of DVT the patients who have RT <21 s.

What is study add?

D-PPG is a useful screening device for the diagnosis of patients with swelling limbs who are clinically suspected DVT of lower limb. In our study, the cut-off points of RT are 19, 20 and 21 s which are results that can be compared with and as acceptable as the previous study. The patients who had RT > 21 s can be excluded DVT. However, patients with RT < 19 s cut-off points who recorded positive test results require further confirmation by duplex ultrasonography.

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Potential conflicts of interest

None.

References

1. Sharif-Kashani B, Behzadnia N, Shahabi P, Sadr M. Screening for deep vein thrombosis in asymptomatic high-risk patients: a comparison between digital photoplethysmography and venous ultrasonography. Angiology 2009; 60: 301-7.
2. Mutirangura P, R□engsethakit C, Wongwanit C. Epidemiologic analysis of proximal deep vein thrombosis in Thai patients: Malignancy, the predominant etiologic factor. Int J Angiol 2004; 13: 81-3.
3. Lam EY, Giswold ME, Moneta GL. Venous and lymphatic disease. In: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Pollock RE, editors. Schwartz's principles of surgery. 8th ed. Philadelphia: McGraw-Hill; 2005: 813-25.
4. Locker T, Goodacre S, Sampson F, Webster A, Sutton AJ. Meta-analysis of plethysmography and rheography in the diagnosis of deep vein thrombosis. Emerg Med J 2006; 23: 630-5.
5. Tovey C, Wyatt S. Diagnosis, investigation, and management of deep vein thrombosis. BMJ 2003; 326: 1180-4.
6. Tan YK, da Silva AF. Digital photoplethysmography in the diagnosis of suspected lower limb DVT: is it useful? Eur J Vasc Endovasc Surg 1999; 18: 71-9.
7. Scarvelis D, Wells PS. Diagnosis and treatment of deep-vein thrombosis. CMAJ 2006; 175: 1087-92.
8. Miles C, Nicolaides AN. Photoplethysmography: principles and development. In: Nicolaides AN, Yao JST, editors. Investigation of vascular disorders. New York: Churchill-Livingstone; 1981: 501-15.

การวินิจฉัย Deep vein thrombosis ด้วย digital photoplethysmographyในผู้ป่วยชาวไทย

เฉนียน เรืองเศรษฐกิจ, ณัฏฐพร นันทิวัฒนา, สุธีคณิต หัถพรสวรรค์, เกียรติศักดิ์ หงษ์คู, ชุมพล วองวานิช, คามิน ชินศักดิ์ชัย, ณัฐวุฒิ เสริมสาธนสวัสดิ์, ประมุข มุธิรางกูร

ภูมิหลัง: Deep vein thrombosis (DVT) ที่ขาพบ 2.5 ถึง 5% ในประชากรของประเทศทางตะวันตก ซึ่งเป็นสาเหตุการเสียชีวิตจาก pulmonary embolism (PE) และความพิการจาก venous ulceration ถ้าไม่ได้รับการรักษาการตรวจด้วย Duplex ultrasonography เป็นมาตรฐาน (sensitivity & specificity >95%) แต่เนื่องจากมีราคาแพงต้องมีผู้เชี่ยวชาญและใช้เวลามากจึงมีข้อจำกัด, Digital photoplethysmography (D-PPG) เป็นการตรวจที่ง่ายไม่ invasive ซึ่งอาจใช้ตรวจเพื่อวินิจฉัย DVT

วัตถุประสงค์: เพื่อศึกษาหาค่า venous refilling time (RT) และ venous pumping (VP) ใน D-PPG ในการวินิจฉัย DVT เมื่อเทียบกับ duplex ultrasonography

วัสดุและวิธีการ: ศึกษาแบบไปข้างหน้าในผู้ป่วย 80 คน (ขาบวม 127 ขา) ที่สงสัยว่าเป็น DVT โดยผู้ป่วยทุกรายได้วัดด้วยเครื่อง D-PPG และ duplex ultrasonography

ผลการศึกษา: ผู้ป่วย 80 คน มีขาบวม 127 ขา, 50 ขา วินิจฉัย DVT จาก duplex ultrasonography ค่า RT ระหว่าง 19 ถึง 21 เป็น optimal cut off point, D-PPG มี sensitivity 95% negative predictive valve 92%, specificity 58% และ positive predictive 52%

สรุป: จากการศึกษาพบว่า D-PPG สามารถใช้เป็นการคัดกรอง (screening test) ในการวินิจฉัย DVT ในรายที่มีอาการ ทางคลินิก (ขาบวม) ในรายที่ให้ผลบวกต้องได้รับการตรวจยืนยันโดย duplex ultrasonography ขณะที่ผลลบ (RT >21) สามารถวินิจฉัยว่าไม่ได้เป็น DVT