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Original Article

Transcutaneous Partial Pressure of Oxygen Measurement in Advanced Chronic Venous Insufficiency as a Marker of Tissue Oxygenation

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Purpose: Determination of oxygen concentration in tissues affected by chronic venous insufficiency (CVI) has shown inconsistent results over the years and has confounded the pathophysiology of venous diseases. This study measured transcutaneous partial oxygen pressure ($TcPO_2$) levels in patients with CVI to assess oxygenation and variation in oxygenation according to CVI stage.

Materials and Methods: A prospective study was performed on consecutive patients with unilateral CVI. $TcPO_2$ of diseased and unaffected limbs was measured in the supine and dependent positions. A single $TcPO_2$ value was measured at the site of greatest skin change or at the edge of the ulcer. The $TcPO_2$ values were analyzed and compared according to stage.

Results: A total of 96 patients were included in the study with C4 (24.0%), C5 (19.8%), and C6 (56.3%) disease. The mean age was 44.7 years, and 85 (88.5%) were male. There was a statistically significant (P<0.01) difference in mean $TcPO_2$ levels between the unaffected limb (supine, 32.1 mmHg; dependent, 50.7 mmHg), C5 diseased limb (supine, 16.6 mmHg; dependent, 35.5 mmHg), and C6 diseased limb (supine, 24.2 mmHg; dependent, 40.4 mmHg). In the supine and dependent positions, the mean $TcPO_2$ in the affected limb was significantly lower (P<0.01) than that in the unaffected limb.

Conclusion: $TcPO_2$ in advanced CVI can be used as a marker of oxygenation status. This is the first study in an Indian population looking at the relevance of $TcPO_2$ in the prognostication of advanced CVI.

Key Words: Venous insufficiency, Varicose veins, Varicose ulcer, Transcutaneous blood gas monitoring

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INTRODUCTION

Chronic venous insufficiency (CVI) commonly affects the lower limbs secondary to valvular incompetence, venous obstruction, or post-thrombotic phenomenon. While CVI is not a life-threatening disease, it can result in long-term morbidity with consequent financial and social implications. Due to a dearth of research on this issue, it is difficult to assess the prevalence of leg ulcers in India, which has a population of over 1.2 billion people [1]. In India, the estimated prevalence of leg ulceration was 4.5/1,000 population, with CVI being a significant contributor; male sex and

intermediate socioeconomic status were found to be risk factors [2,3].

Adequate tissue perfusion and oxygenation are prerequisites for wound healing. Factors hampering tissue oxygenation predispose patients to ulcer formation and persistence. In CVI, the microcirculation is impaired, resulting in skin changes and ulcer formation. There are few studies with conflicting results documenting the correlation between CVI and tissue oxygen [4-7], with none in the Indian population in the English literature. Tissue oxygenation can be estimated by measuring transcutaneous partial oxygen pressure ($TcPO_2$).

Measurement of oxygen tension in the tissue is a good tool for predicting wound healing post-amputation in arterial diseases [8]. In this study, $TcPO_2$ in advanced CVI (stages C4 to C6) was measured and compared to the $TcPO_2$ in the unaffected limb. Measurement of tissue oxygenation (hypoxia) in CVI using $TcPO_2$ can help to better understand the disease process, prognostication, and compare the effectiveness of various treatment modalities. We hypothesized that tissue oxygenation, as represented by $TcPO_2$, will progressively decrease from C4 to C6 according to the CVI severity.

MATERIALS AND METHODS

This prospective cross-sectional study was conducted at our teaching hospital between July 2014 and August 2016. The study was approved by the Institutional Review Board of the Christian Medical College (IRB no. 8994) and written informed consent was obtained from the patients. Based on the formula $(1.96)^2 \times pq/d^2$ for observational cross-sectional prospective study, the required sample size was calculated to 96 ("p," i.e., prevalence, was taken to be 50%; "q" = p-1; and "d" is the standard error [10%]) [9].

Patients presenting to the vascular surgery department with unilateral CVI, C4 to C6, were screened and included in the study. All patients underwent duplex ultrasonography. Twenty-two patients were excluded from the study after screening because of bilateral limb disease, peripheral arterial disease, vasculitis, active limb infection, or pedal edema due to other causes (lymphedema, renal, or hepatic failure). C3 disease was also excluded because edema is known to alter the $TcPO_2$ value [10]. The contralateral limb did not show any clinical symptoms or signs of CVI.

After obtaining informed consent, a detailed clinical examination was performed to confirm the diagnosis of CVI, stage the disease according to the Clinical-Etiology-Anatomy-Pathophysiology classification [11], and rule out other causes of limb ulcers. A single $TcPO_2$ measurement was taken in the supine and dependent (sitting) positions at the site of maximum skin change since it would reflect the lowest level of oxygenation corresponding to the site of maximal microangiopathic changes or the worst disease. In C6 disease, $TcPO_2$ was measured close to the ulcer edge, while in C5 disease, it was measured close to the border of the scarred tissue. The $TcPO_2$ value at the corresponding site of the opposite limb served as an internal control for that particular patient, thus matching patient-related confounding factors. Measurements were obtained in the vascular lab at an ambient temperature of 22°C to 24°C. The electrode was attached with an adhesive ring to the site at a temperature of 43°C. The physiological stabilization time of a patient is 15 to 20 minutes for $TcPO_2$ reading. During this time, the electrode slowly heats the skin and dilates the arteries. The stable value after 20 minutes was recorded as the measurement for the analysis.

Data were analyzed using IBM SPSS statistics (version 21.0; IBM Corp., Armonk, NY, USA). Descriptive statistics, paired t-test, independent samples t-test, and Bonferroni analysis were performed. Statistical significance was set at $P<0.05$.

RESULTS

Of the 96 patients, 59.4% were above the age of 40 years (mean age, 44.7±11.7 years; range, 25-73 years). The study included 85 males and 11 females. Left-sided disease was present in 51 (60.0%) males and 7 (63.6%) females (Table 1).

A Shapiro–Wilk test and visual inspection of histograms, normal Q-Q plots, and box plots showed that the $TcPO_2$ values of the affected and non-affected limbs were normally distributed when measured in the dependent position (skew-

Table 1. Descriptive statistics of patients included in study

Characteristic	Male (n=85)	Female (n=11)	Total (n=96)
Stage			
C4	20 (23.5)	3 (27.3)	23 (24.0)
C5	18 (21.2)	1 (9.1)	19 (19.8)
C6	47 (55.3)	7 (63.6)	54 (56.3)
Side			
Right	34 (40.0)	4 (36.4)	38 (39.6)
Left	51 (60.0)	7 (63.6)	58 (60.4)
Age (y)			
≤30	11 (12.9)	2 (18.2)	13 (13.5)
31-45	36 (42.4)	1 (9.1)	37 (38.5)
46-60	31 (36.5)	6 (54.6)	37 (38.5)
>60	7 (8.2)	2 (18.2)	9 (9.4)

Values are presented as number (%).

Table 2. Comparison of supine and dependent mean $TcPO_2$ values in unaffected and affected limbs

Limb	Position	$TcPO_2$ (mmHg)	Paired t-test
Normal	Supine (I)	32.05±11.16	
	Dependent (J)	50.74±11.89	
	Difference (J–I)	18.69±6.83	P<0.01
Diseased	Supine (I)	23.28±11.52	
	Dependent (J)	40.50±12.22	
	Difference (J–I)	17.12±6.68	P<0.01

Values are presented as mean±standard deviation.

Table 3. Comparison of mean $TcPO_2$ in different stages of CVI and their significance in different positions (unit: mmHg)

Position	CVI stage (I) (mean $TcPO_2$)	CVI stage (J) (mean $TcPO_2$)	Mean $TcPO_2$ difference (I–J)	P-value
Supine	C0 (32.05)	C4 (26.57)	5.48	0.187
		C5 (16.63)	15.42	<0.001*
		C6 (24.22)	7.83	<0.001*
	C4 (26.57)	C5 (16.63)	9.94	0.022*
		C6 (24.22)	2.34	>0.999
	C5 (16.63)	C6 (24.22)	–7.59	0.058
Dependent	C0 (50.74)	C4 (44.83)	5.91	0.182
		C5 (35.47)	15.27	<0.001*
		C6 (40.43)	10.31	<0.001*
	C4 (44.83)	C5 (35.47)	9.36	0.063
		C6 (40.43)	4.40	0.791
	C5 (35.47)	C6 (40.43)	–4.96	0.681

CVI, chronic venous insufficiency.
*Statistically significant.

ness<0.35), but had significant skewness when measured in the supine position (affected limb, 0.729; non-affected limb, 0.814). However, parametric tests were employed in all cases, as they fulfilled the other required conditions for parametric tests.

In the supine position, irrespective of the stage of advanced CVI, the mean $TcPO_2$ in the affected limb (23.3 mmHg) was significantly lower than that in the non-affected limb (32.1 mmHg; P<0.01). In the dependent position, the $TcPO_2$ in the affected limb (40.5 mmHg) was significantly lower than that in the non-affected limb (50.7 mmHg; P<0.01; Table 2).

Subgroup comparison according to the affected legs of various stages versus the unaffected leg (Table 3) showed a statistically significant difference between the unaffected leg and legs with stage C5 to C6 disease (P<0.01). The difference in $TcPO_2$ was statistically non-significant for C4 disease. However, the values were lower in legs with C5 or C6 disease, both in the supine and dependent positions (Table 3). In the supine position, a statistically significant decrease in mean $TcPO_2$ values was observed between C4 and C5, but not between C5 and C6. This decrease was not significant among stages C4 to C6 in the dependent position. The range of $TcPO_2$ values is listed in Table 4.

Table 4. Range of $TcPO_2$ in clinical stages 4, 5, 6 and normal limb (unit: mmHg)

Clinical stage	Position	
	Supine	Dependent
Stage 4 $TcPO_2$ (n=23)		
Mean±SD	26.57±13.59	44.83±13.05
Median (range)	28.00 (6–65)	49.00 (22–75)
SEM	2.97	2.85
Stage 5 $TcPO_2$ (n=19)		
Mean±SD	16.63±8.80	35.47±9.95
Median (range)	18.00 (4–32)	35.00 (15–52)
SEM	2.14	2.41
Stage 6 $TcPO_2$ (n=54)		
Mean±SD	24.22±10.43	40.43±12.00
Median (range)	24.50 (1–54)	43.00 (4–60)
SEM	1.61	1.85
Normal limb $TcPO_2$ (n=96)		
Mean±SD	32.05±11.16	50.74±11.89
Median (range)	30.00 (5–74)	50.00 (20–85)
SEM	1.25	1.33

SD, standard deviation; SEM, standard error of the mean.

The $TcPO_2$ had fair accuracy with an area under the receiver operating characteristic curve >0.7 for both supine (Fig. 1) and dependent positions (Fig. 2) in detecting advanced CVI, when compared to the unaffected limb. A $TcPO_2$ value of 40 mmHg in the supine position had a sensitivity of 95% and specificity of 20% for predicting the diseased state. In the dependent position, a value of 56 mmHg had a sensitivity of approximately 91%, with a specificity of 25%. A cut-off value could not be recommended because the increase in sensitivity was at the expense of specificity and a high false-positive rate. There was a positive correlation between supine and dependent $TcPO_2$ values in both affected (0.839) and non-affected (0.818) limbs (Fig. 3).

DISCUSSION

The transcutaneous oxygen content is supposed to reflect the microcirculatory state of the underlying tissue, both in health and disease. Its content or partial pressure should decrease with severe disease in CVI, with values being lowest in stage C6, with or without trophic changes. A

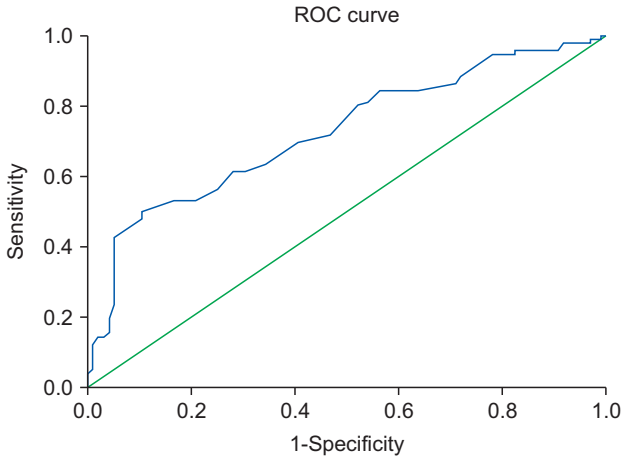

Fig. 1. Receiver operating characteristic (ROC) of supine $TcPO_2$ in predicting disease state. Area under the curve=0.727, standard error=0.036, P<0.001.

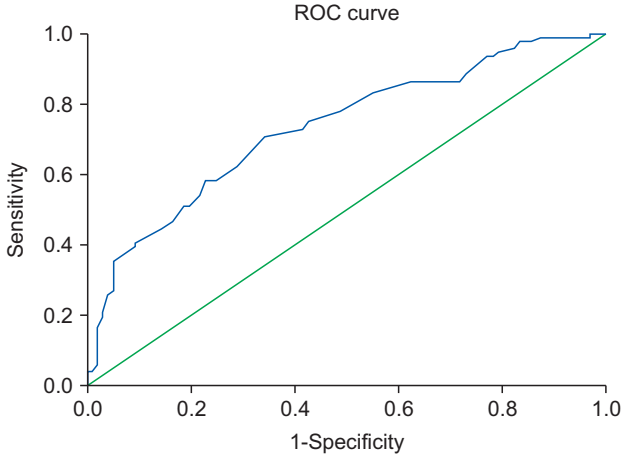

Fig. 2. Receiver operating characteristic (ROC) of dependent $TcPO_2$ in predicting disease state. Area under the curve=0.733, standard error=0.036, P<0.001.

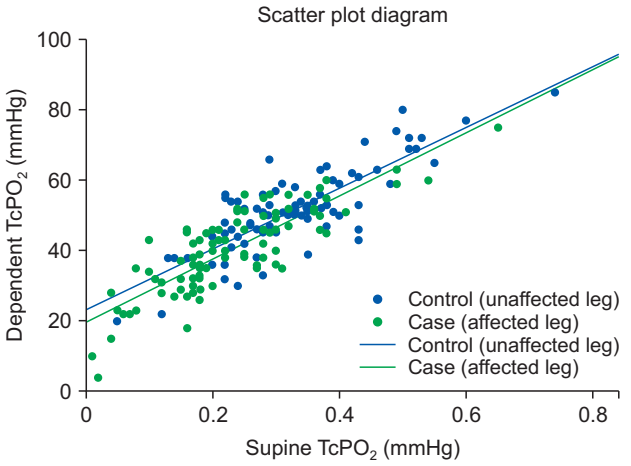

Fig. 3. Scatter plot of supine and dependent $TcPO_2$ values in affected and unaffected legs. Control R^2 linear = 0.669. Case R^2 linear = 0.703.

higher $TcPO_2$ would indicate a better state of health in the tissue. The null hypothesis would state that $TcPO_2$ does not reflect the microcirculation the CVI.

The prevalence of CVI is higher in females, as seen in many population studies [9,12]. However, this study of 96 Indian patients included 85 males (88.5%) and 11 (11.5%) females, and the prevalence of CVI was lower in females, which may reflect a selection bias. The prevalence of CVI increases with age [13]. In this study, 59.4% of patients were above the age of 40 years. $TcPO_2$ had fair accuracy in detecting advanced stage CVI (C4 to C6) when compared to the unaffected limb. The values were significantly lower in the C5/C6 disease, both in the supine and dependent positions. Segregated by stage, $TcPO_2$ was significantly lower in C5/C6 than in the unaffected limb. C6 had a statistically non-significantly higher $TcPO_2$ than that of C5. There was a significant decrease in $TcPO_2$ from C4 to C5. This is expected because scarred or healed lesions are known to have low oxygen tension.

In a study by Franzeck et al. [14], $TcPO_2$ was measured and correlated with video microscopy to examine the microvasculature. The mean $TcPO_2$ of control group was 56.8 mmHg, and that of affected group was 47.7 mmHg. The difference was not statistically significant (P>0.05). In this study, $TcPO_2$ was measured at the site of maximal change, which reflects poor microcirculation internally.

Barnikol and Pötzschke [15] reported a comparative study of the mean value of four $TcPO_2$ measurements in patients with C6 CVI; the mean $TcPO_2$ value was significantly lower in the C6 disease group than in the control group (17.9 vs. 63.0 mmHg, respectively). In this study, the mean $TcPO_2$ was also significantly lower in the C6 disease group than in the control group (24.2 vs. 32.1 mmHg, respectively). The greater difference in the mean values in the study by Barnikol and Pötzschke [15] was probably due to four measurements taken around the ulcer, which is more reliable than a single measurement. However, even a single measurement at the site of greatest skin change was statistically significant, as shown in this study. Recently, $TcPO_2$ was also studied in post-thrombotic syndrome (PTS) by Cuen-Ojeda et al. [16], who found low $TcPO_2$ levels in severe cases of PTS.

A cutoff value of 40 mmHg in the supine position had 95% sensitivity and 20% specificity; the same cutoff in the dependent position had a 50% sensitivity and 80% specificity. A particular cutoff value could not be recommended, as the increase in sensitivity came at the expense of specificity and a high false-positive rate. The study also

found that the $TcPO_2$ was significantly lower in the supine position than in the dependent position, thus demonstrating the effect of limb position on $TcPO_2$ values.

There are several limitations to this study. The number of patients in each stage of advanced CVI was not equal, with the majority of patients in the C6 stage. A single periarticular $TcPO_2$ measurement may not provide representative information concerning the oxygen status of the entire wound due to oxygen inhomogeneity. Multiple same-limb control measurements were not performed. However, this was primarily done to determine whether $TcPO_2$ correlates with the severity of CVI. In addition, repeated measurements would take time and add expense due to the need for new electrodes, which is difficult in resource-limited settings. There could be a potential selection bias, as the location for $TcPO_2$ measurement was based on the subjective assessment of area of maximum skin change. Peripheral arterial disease was ruled out in all patients clinically with the presence of palpable pulses and normal ankle-brachial pressure index; however, an arterial duplex ultrasound was not performed in all patients.

In a limb affected by CVI, the $TcPO_2$ was significantly lower in the C5/C6 stage than in the unaffected limb, with a definite effect of limb positioning on $TcPO_2$ values. Since $TcPO_2$ was lowest in the C5 stage, its role or clinical relevance in this stage is doubtful, as scarred tissue will obviously have low oxygen tension. The statistically significantly lower value than that in the unaffected limb and the decrease in $TcPO_2$ from C4 to C6 (though not statistically significant) provides a direction for studies focusing on single $TcPO_2$ value as a prognostic tool in relation to interventions and as a marker for C6 disease. An increase in $TcPO_2$ following intervention could predict the efficacy of the intervention. Future studies using $TcPO_2$ to compare interventions or objectively assess improvement after an intervention can be conducted.

CONCLUSION

$TcPO_2$ is a non-invasive test that can be used with a single value in an outpatient setting to assess clinical progression (worsening or improvement) of CVI. This is the first study in an Indian population focusing on the relevance of $TcPO_2$ in advanced CVI for prognostication.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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Concept and design: AAK, SA. Analysis and interpretation: LJ, AAK, SA. Data collection: LJ, AAK. Writing the article: LJ, AAK. Critical revision of the article: LJ, AAK, VS, PP, DS, ES, SA, PG. Final approval of the article: all authors. Statistical analysis: LJ, AAK. Obtained funding: LJ, AAK. Overall responsibility: AAK.

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