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Comparison of Photo-optical Transcutaneous Oxygen Tension Measurement with Electro-chemical Transcutaneous Oxygen Tension Measurement in Patients with Arterial Claudication

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Purpose: Photo-optical TCpO2 (pTCpO2) has been proposed as a new method to determine the partial oxygen pressure of the lower extremity in patients with peripheral arterial disease. It is aimed to determine the level of agreement between pTCpO2 and the traditional electro-chemical transcutaneous oxygen tension measurement (eTCpO2).

Methods: Eighteen patients with intermittent claudication underwent simultaneous ankle-brachial index measurement, toe-pressure, pTCpO2 and eTCpO2 tests. Oxygen tension levels were measured on anterior chest and calf prior in rest (T0), during induced ischemia (T1) and after blood flow restoration (T2). TCpO2 agreement was assessed according to the principles of Bland and Altman.

Results: Absolute average TCpO2 values differed between eTCpO2 and pTCpO2 for calf in T2 (38,1 mmHg (σ 14,4) vs. 49,8 (σ 22.3) with $P = 0.35$). The Bland-Altman plots demonstrated eTCpO2 and pTCpO2 bias of 3,7 mmHg (σ 18,8), 11,6 mmHg (σ 17,6) and 6,7 mmHg (σ 23,5) for T0, T1 and T2 for the calf.

Conclusion: pTCpO2 is in agreement with eTCpO2 in measuring pO2 levels of the lower extremity in rest and during induced ischemia in patients with vascular claudication. The large variability between eTCpO2 and pTCpO2 should be accounted for, while pTCpO2 values have a tendency to demonstrate higher values in comparison to eTCpO2.

INTRODUCTION

Electro-chemical transcutaneous oxygen tension measurement (eTCpO2) has been applied for decades to deduce the partial oxygen pressure of underlying skin tissue. The clinical application of eTCpO2 has extended from determination of oxygen status of neonates[1], skin flap healing prognosis[2] to the evaluation of diabetic foot ulcer healing prognosis[3] and chronic limb-threatening ischemia (CLTI) assessment.[4] Recently, a novel photo-optical approach of TCpO2 measurement (pTCpO2) for the lower extremity has been introduced.[5] Photo-optical TCpO2 has been proposed as a more reliable form of TCpO2 as it does not consume nor extract oxygen.[2,6,7] Besides, pTCpO2 is suggested to be more practical, primarily because it is less time consuming.[5] Also, pTCpO2 devices are significantly cheaper to purchase in comparison to eTCpO2 ($2500 vs.

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$15.000), therefore more accessible in primary care centres. However, to date only one clinical study examined pTCpO2 and showed a relative correlation between pTCpO2 and eTCpO2. Yet, the level of agreement between the pTCpO2 and eTCpO2 remains unknown. Providing a real-time deduction of the vascular status during induced ischemia, with treadmill test, might be beneficial in the search for new non-invasive diagnostic tests to determine the severity of the vascular claudication. To explore if real-time measurement of photo-optical TCpO2 is feasible when patients with peripheral arterial disease undergo a treadmill test and to demonstrate the level of agreement between pTCpO2 and eTCpO2 measurement we conducted a explorative comparative study.

MATERIAL AND METHODS

Study Population

Consecutive patients with suspected peripheral arterial disease symptoms and whom were referred to the vascular laboratory for non-invasive vascular testing between January and March 2018 in the Jeroen Bosch Hospital, Den Bosch, The Netherlands, were approached to participate in this study. Patients were included if they suffered at least Fontaine stage 2 symptoms with an exercise ABI of <0.8 measured on the right extremity. Written informed consent was obtained from all participating patients. This study was approved by the local Medical Ethical Committee. Sample size was calculated with $\alpha = 0.05$, $\beta = 0.20$, expected mean differences = 10, expected σ of differences = 10, maximum allowed difference between methods = 50, demonstrated minimal required sample size of 10.

Non-invasive Vascular Testing

To accurately visualize differences in measurement between both TCpO2 devices we choose for continuous TCpO2 monitoring during induced local ischemia. Therefore, patients conducted a treadmill test with continuous electro-chemical and photo-optical TCpO2 monitoring. The eTCpO2 probe consists of a Clark-electrode, this electrode reduces oxygen molecules electrolytically and generates a current from which partial oxygen pressure is deduced. pTCpO2 derives the oxygen partial pressure based on the interaction of light and matter. Oxygen molecules undergo a phase-shift when in contact with light at a specific wave-length. In turn, this phase-shift causes oxygen molecules to reflect light at a different specific wave-length. this excitation light is captured by a wavelength-filtered photodetector. Both TCpO2 devices provide oxygen pressure in mmHg.[7]

The treadmill was set at a 3.2 km/h walking speed with 10% slope for ten minutes. During treadmill exercise continuous pTCpO2 and eTCpO2 recordings were measured and noted at rest (T0), at 10 minutes or termination due to pain or fatigue felt by patients (T1) and at five minutes after treadmill test termination (T2). All non-invasive vascular measurements were carried out by the same experienced vascular-laboratory technician. ABI and TP measurement were conducted according to standard operating protocol with visual Doppler measurement and oxygen-saturation (SO2) was measured on the index finger with pulse oximetry. The electro-chemical TCpO2 measurement device (TCM 400, Radiometer®, Krefeld, Germany) and photo-optical TCpO2 measurement device (Précise 8008 MediCap®, Ulrichstein, Germany) were set to default temperature at 44 degrees Celsius. Room temperature was measured prior to each measurement. The eTCpO2 device was calibrated prior to each patient measurement and probes were inspected for the occurrence of gas bubble formation after each measurement. One TCpO2 probe of each device was placed on the right calf of the subject after cleansing of the skin and avoiding underlying tendon or superficial venous structures. An image of this setup is demonstrated in image l. Probes were attached firmly to the calf with bandage to avoid disconnection during the treadmill test. Reference TCpO2 probes of both devices were placed on the right side of the anterior chest. Baseline ABI, TP, SO2, at probe site and TCpO2 values were measured with patient resting in supine position.

Statistical Analysis

Descriptive statistics were used to present baseline characteristics. Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as means and SDs, as TCpO2 data was normally distributed. As eTCpO2 and pTCpO2 measure the same variable, both measurement devices provide a derivative of the present oxygen pressure and there is no diagnostic tool that can serve as a golden standard we compared the level of agreement between eTCpO2 and pTCpO2 with Bland and Altman plots.[8] Pearson's test for correlation was used to compare ABI, TP, SO2 with eTCpO2 and pTCpO2. Data analysis was conducted using Statistical Package for the Social Sciences (SPSS®; version 25 IBM, Armonk, NY, U.S.A.)

Table l. Baseline characteristics

Baseline characteristics	
Gender (female/male)	7/11
Mean age	70,8 (σ 7,9)
Ankle-brachial index (in rest)	0,8 (σ 0,27)
Toe-pressure (in rest, mmHg)	68 (σ 19,7)
Saturation (SO2) (in rest, %)	97,5 (σ 0,7)
Fontaine classification	
2A	6 (33 %)
2B	12 (67 %)
Smoking status Active smoker	
Active smoker	7 (39 %)
Former smoker	11 (61 %)
Body Mass Index	
< 20	1 (5 %)
20-25	3 (17 %)
25-30	11 (61 %)
30-40	3 (17 %)
Diabetes mellitus	5 (28 %)
Heart disease	2 (11 %)
Pulmonary disease	0 (0 %)
Dyslipidemia	15 (83 %)
Anti-platelet drugs	10 (56 %)
Anti-coagulation drugs	0 (0 %)

and GraphPad (Prism®; version 7.04, GraphPad Software, Inc.)

RESULTS

In total, twenty-five patients were included. Seven patients scheduled for participation did not meet the inclusion criteria, ABI of <0.8 measured on the right extremity, and were excluded. Eighteen patients underwent vascular tests. During treadmill exercise (T2) probes disconnected in five patients and these measurements were excluded. An overview of baseline characteristics is demonstrated in Table l. Significant difference was found between eTCpO2 and pTCpO2 mean value for calf in T2 (38,1 mmHg (σ 14,4) vs. 49,8 (σ 22,3) with $P = 0.04$). Mean TCpO2 values are demonstrated in Table 2. Bland-Altman plots demonstrate a bias between eTCpO2 and pTCpO2 for the anterior chest of 4,3 mmHg (σ 27,3), 6,2 mmHg (σ 18,9) and 7,1 mmHg (σ 23,6) and for the calf 3,7 mmHg (σ 18,8), 11,6 mmHg (σ 17,6) and 6,7 mmHg (σ 23,5) for T0, T1 and T2, respectively. An overview of the Bland-Altman plots is demonstrated in Fig. l. A weak positive correlation was found in T0 between toe-pressure and calf eTCpO2 ($r = 0.48$ $P = 0.04$). A moderate negative correlation was found in T0 between SO2 in rest and pTCpO2 ($r = -0.6$ $P = 0.009$).

DISCUSSION

In this explorative comparative study, we demonstrated the level of agreement between electro-chemical TCpO2 (eTCpO2) and the novel photo-optical TCpO2 (pTCpO2) to determine partial oxygen pressure in patients with vascular claudication. As demonstrated in the Bland-Altman plots (Figure l), dots were sufficiently equally present above and below the mean, the mean was close to zero and 95% of the dots lie within two standard deviations. There is, to our knowledge, no known acceptable limit of bias between TCpO2 measurements. However, commonly TCpO2 values are interpreted and categorized within margins of 10 mmHg.[4] Therefore, our demonstrated bias indicates an acceptable agreement between eTCpO2 and pTCpO2. Nevertheless, we found large standard deviations as the dots are not clustered close to the mean, this indicates notable variability between eTCpO2 and pTCpO2 measurements. Thus, it could be concluded that some TCpO2 measurements should be considered unreliable. However, as the exact partial oxygen pressure is unknown it is impossible to determine which TCpO2 measurement was inaccurate. pTCpO2 measurements have a tendency to demonstrate higher mmHg values in comparison to eTCpO2. A possible explanation for this could be the temperature sensitive Clark-electrode present in the eTCpO2 probe, the Clark electrode consumes oxygen to allow a current to flow which is corresponding to partial oxygen pressure.[9] Yet, the exact influence of temperature and Clark-electrode consumption of oxygen molecules on mmHg values in eTCpO2 measurement outcome is unknown.[10,11] pTCpO2 does not consume oxygen, the principle of photo-optical pO2 measuring is explained elsewhere[6]. The absolute mmHg values difference between pTCpO2 and eTCpO2 is of importance when applying pTCpO2 values in clinical classification systems designed for eTCpO2 values. This study has some limitations. In general, TCpO2 measurements are easily affected. TCpO2 probes are sensitive to moist, temperature, gas leakage and also underlying venous and bony structures might alter measurement outcome.[10-12] Therefore, this sensitivity of TCpO2 probe measurement does challenge the reliability of TCpO2 measurement to some extent. Moreover, vibrations of the probe generated with the treadmill test also might have altered measurement outcome. This could explain the outliers in our measurement data, demonstrated in the Bland-Altman plots. This limitation could have been

Table ll. Mean TCpO2 values

	Available pairs (n)	eTCpO2 mean mmHg (σ)	pTCpO2 mean mmHg (σ)	P
Anterior chest				
T0	18	61,7 (22,3)	66,1 (13,4)	0.51
T1	13	62,1 (13,2)	68,3 (13,6)	0.26
T2	18	62,2 (19,8)	69,3 (13,5)	0.22
Calf				
T0	18	54,1 (14,9)	57,7 (16,9)	0.42
T1	13	38,1 (14,4)	49,8 (22,3)	0.04
T3	18	40,3 (17,5)	47,1 (23,7)	0.24

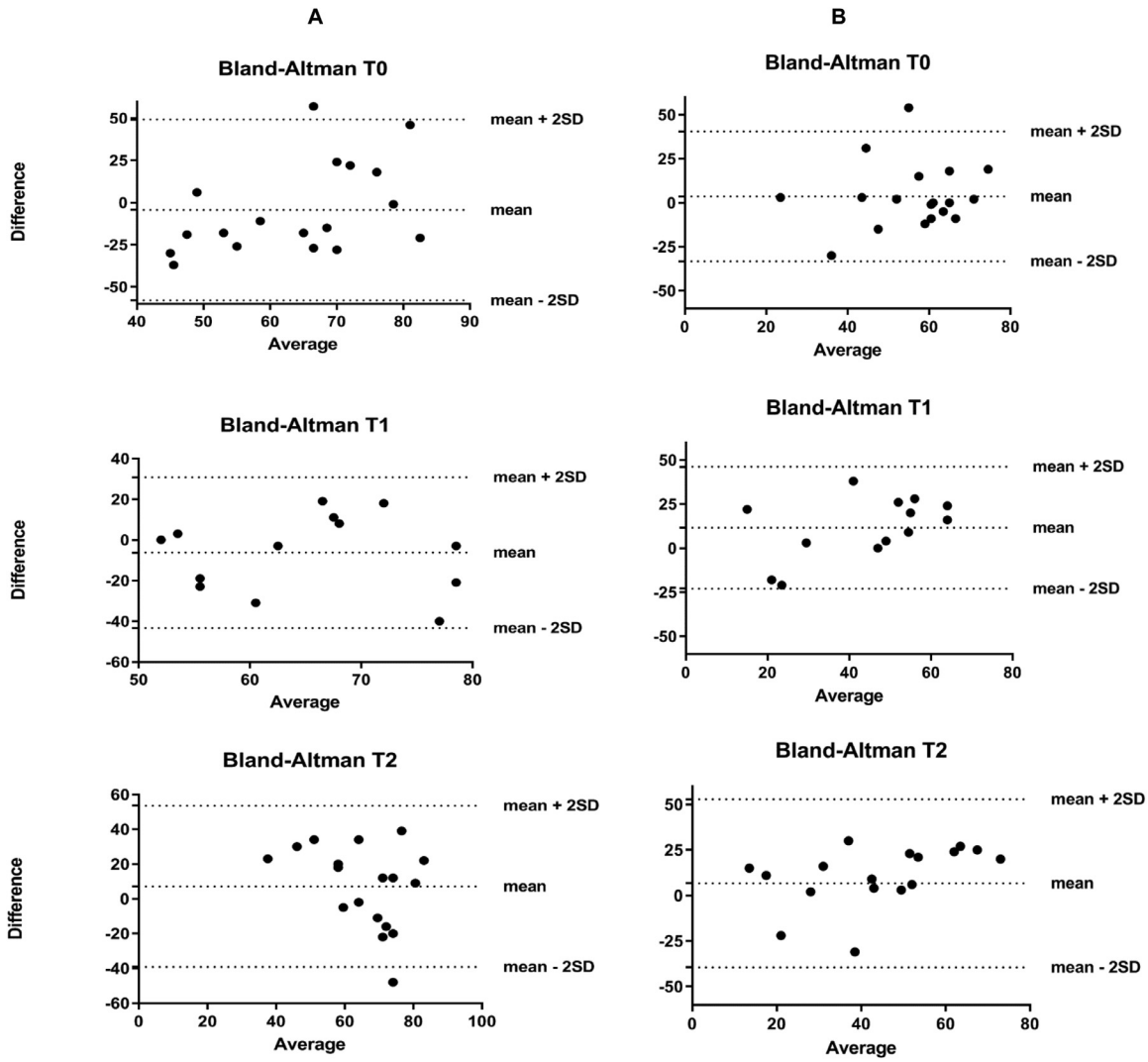

Fig. l. Bland-Altman plots for anterior chest and calf. (A) Bland-Altman plots of the anterior chest at T0, T1 and T2. Difference is eTCpO2 – pTCpO2 (in mmHg) and average is mean of eTCpO2 and pTCpO2 (in mmHg).(B) Bland-Altman plots of the calf at T0, T1 and T2. Difference is eTCpO2 – pTCpO2 (in mmHg) and average is mean of eTCpO2 and pTCpO2 (in mmHg).

overcome if both TCpO2 devices simultaneously and directly measured patients with chronic limb-threatening ischemia (CLTI) in rest. However, we also wanted to explore the effect the feasibility of real-time TCpO2 measurement during treadmill test. Inducing ischemia and treadmill testing is not suitable in patients with CLTI. As eTCpO2 and pTCpO2 have different technical method of measurement, real-time monitoring during locally induced ischemia was desired in an attempt to make potential differences better detectable. However, with multiple probes disconnected during the treadmill test it can be concluded that real-time TCpO2 monitoring during a treadmill test is not recommended. Still, the Bland-Altman plots demonstrate an acceptable agreement. The present study was conducted with a small sample size, although within the limit of the sample size calculation. A larger study population could have resulted in less effect of outliers on the mean differences and standard deviations. However, if these limitations would have been overcome this would not alter our results significantly. One other comparable clinical study also found higher pTCpO2 values in comparison to eTCpO2 values, they demonstrated a strong correlation between pTCpO2 and eTCpO2.[5] However, when comparing two measurement systems that measure the same value on the same subject the use of correlation as a statistical method is not recommended.[13] Correlation is used to determine the relationship between two different constructs.[14] The Bland-Altman plots are a well-established and known statistical method to determine level of agreement between two comparable measurement devices. pTCpO2 has an acceptable agreement with eTCpO2 and therefore could serve as an alternative to the conventional eTCpO2 measurement for patients with peripheral arterial disease. Although, caution is warranted when interpreting pTCpO2 values due to its tendency to demonstrate higher mmHg values in comparison to eTCpO2.This is especially important when applying pTCpO2 values in wound classification systems designed for eTCpO2 values, such as the WiFi classification. As pTCpO2 is suggested to be more practical in use, cheaper in purchase and as we now demonstrated in concordance with eTCpO2, more primary and secondary centres could access TCpO2 measurement. For instance, as pTCpO2 is significantly cheaper in purchase more (primary) care centres could acquire a TCpO2 measurement device, therefore more CLTI patients could receive TCpO2 measurement and potentially ease delay in referral specialized vascular centres. The reliability of TCpO2 measurement during treadmill test is debatable.

CONCLUSION

Photo-optical TCpO2 demonstrated an acceptable agreement in comparison to electro-chemical TCpO2 measurements in patients with peripheral arterial disease. However, a large variability in measurements should be noted. Photo-optical mmHg values are in general higher in comparison to electro-chemical TCpO2 values. Real-time TCpO2 measurement during treadmill test is not recommended. More research is warranted to determine the added value of photo-optical TCpO2 for the diagnosis and evaluation of peripheral arterial diseases.

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