Microvascular Research 116 (2018) 15–19

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

# Peripheral circulatory disorders in essential thrombocythemia

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ARTICLE INFO

*Article history:*
Received 9 January 2017
Revised 5 May 2017
Accepted 6 May 2017
Available online 07 May 2017

*Keywords:*
Essential thrombocythemia
Microcirculation
Pulse wave
Peripheral resistance

ABSTRACT

A significant number of patients with essential thrombocythemia (ET) complain of symptoms including distal parts of the extremities (e.g., paresthesias or Raynaud's phenomenon). The aim of the present study was to examine peripheral circulation in the upper extremities of individuals with ET. The study included 45 ET patients and 30 control subjects. All participants were subjected to thermography, photoplethysmography, impedance plethysmography, and applanation tonometry pulse wave analysis. The patients with ET differed significantly from the control subjects in terms of 3rd finger skin temperature (mean 31.04 vs. 32.45 °C), skin temperature gradient (mean 1.82 vs. 0.11 °C), photoplethysmographic amplitude (median 0.25 vs. 0.74%), and pulse waveform in the radial artery (more frequent occurrence of type B waveform). Pulse wave parameters correlated with the skin temperature gradient. The study findings imply the altered regulation of peripheral circulation in ET, including a decreased flow and an increased resistance.



## 1. Introduction

Essential thrombocythemia (ET) belongs to the group of BCR-ABL-negative myeloproliferative neoplasms. The incidence of this condition ranges from 0.38 to 1.7 per 100,000 annually (Tefferi et al., 2009). In some authors' opinion, the thrombotic complications of ET constitute a more important clinical problem than bleeding tendencies as they may occur in up to 6.6% of patients annually (in the same study, the incidence of bleeding was only 0.33%) (Petrides and Siegel, 2006).

Microcirculation may be affected in the course of the disease, resulting in such symptoms as headaches, paresthesias and vasomotor disorders (erythromelalgia, livedo reticularis and Raynaud's phenomenon). In the study including 267 patients with ET neurological symptoms not related to large-vessel thrombosis were observed in 35.8% of the cases: up to 53.5% among these patients reported persistent headaches and 43.5% suffered from paresthesias (Aroldi et al., 2016). The disturbances may result from platelet activation and aggregation and occur primarily in the arterioles as a consequence of high shear stress peculiar to this vascular bed.

To the best of our knowledge, few published studies have concerned peripheral circulation in ET patients, and the available data on limb perfusion and peripheral resistance are sparse. The aim of the present study was to verify if ET patients differ from healthy individuals in terms of objective parameters of upper extremity perfusion and peripheral resistance.

## 2. Material and methods

The cross-sectional study included 45 individuals with established diagnosis of ET and 30 healthy controls. The exclusion criteria were: anticoagulant therapy, presence of concomitant neoplasms other than ET, renal failure (serum creatinine > 177 μmol/L), hepatic injury (alanine aminotransferase activity > 90.0 U/L) and signs of active infection. The study was conducted in line with the provisions of the Helsinki Declaration, after obtaining approval from the Local Bioethics Committee and collecting written, informed consent from all participants. ET was diagnosed according to WHO criteria (Tefferi et al., 2009).

The median time elapsed since the diagnosis of ET was 7.5 years (interquartile range, IQR: 2.0–11.0), and median platelet count in the ET group was $473 \times 10^3$/μL (IQR: 405–549 $\times 10^3$/μL). A total of 18 subjects were treated with anagrelide, 10 with hydroxyurea, 6 with both these agents, 3 with interferon α2b, 2 with pipobroman; 6 patients did not receive any cytoreductive treatment. Acetylsalicylic acid was administered to 33 patients, ticlopidine and clopidogrel to 2 and 1, respectively; 9 subjects did not receive any anti-platelet treatment because of contraindications. Eleven patients (24.4%) reported persistent paresthesia of the hands and/or feet. None of the controls were treated for chronic conditions or took any medications. ET patients did not differ from the controls in terms of their sex distribution, age, cigarette

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https://doi.org/10.1016/j.mvr.2017.05.002
0026-2862/

**Table 1**
Demographic and clinical characteristics of patients with essential thrombocythemia (ET) and the controls. Values are presented as numbers, means ± standard deviations, or medians and interquartile ranges. P — *P*-value for difference between groups.

| Variable | ET group | Control group | P |
|---|---|---|---|
| Sex (male/female) | 10/35 | 12/18 | 0.098 |
| Age (years) | 56.25 ± 13.14 | 54.60 ± 8.59 | 0.469 |
| Cigarette smoking (yes/no) | 41/4 | 23/7 | 0.083 |
| Body mass index (kg/m$^2$) | 25.25 ± 3.52 | 25.49 ± 3.91 | 0.509 |
| Systolic blood pressure (mm Hg) | 128.07 ± 16.92 | 129.36 ± 19.64 | 0.778 |
| Diastolic blood pressure (mm Hg) | 74.84 ± 11.96 | 77.12 ± 8.25 | 0.396 |
| Platelet count (×10$^3$/μL) | 473 (405–549) | 252 (217–308) | 0.000 |

smoking, body mass index, systolic nor diastolic blood pressure (Table 1).

All participants were subjected to infrared thermography, reflectance-mode photoplethysmography, impedance plethysmography and peripheral pulse wave analysis.

### 2.1. Infrared thermography

Skin temperatures were determined with a thermal imaging camera IC060 (Trotec GmbH) dedicated to measurement of the body and objects (measuring range: −20 to 250 °C, thermal sensitivity: 0.1 °C at 30 °C, geometric resolution 2.2 mrad). The measurements were taken after a 10-min rest in a warm and quiet place. Mean values from repeated measurements were calculated. The measurements were taken from the palmar surface of the metacarpus and palmar surface of the 3rd finger distally from the proximal interphalangeal joint. The 3rd finger was subjected to analysis due to the origin of the common palmar digital arteries in the superficial palmar arch and less dependence on blood supply from the radial or ulnar artery (Al-Turk and Metcalf, 1984). The examination was conducted in line with the European Association of Thermology (EAT) standards (Howell and Smith, 2009).

### 2.2. Photoplethysmography

Reflectance-mode photoplethysmography is a method for peripheral circulation assessment in which a beam of light emitted by a diode and reflected by the tissues is registered (Reisner et al., 2008). After a 5-min rest, photoplethysmographic recordings were performed on fingertips. After determining the start, peak and end of the photoplethysmographic wave, mean values of the following parameters were determined for both thumbs: (1) pulse amplitude (PA), (2) peak time (PT), i.e. the time from the start of the wave to its peak, (3) decline time (DT), i.e. the time from the peak of the wave to its end. Also the PT/DT ratio was calculated. All measurements were taken with a Vasolab 5000 device (Elcat GmbH).

### 2.3. Impedance plethysmography

Impedance plethysmography (rheography) is a method to analyze changes in tissue resistivity resulting from exposure to alternating electric current. Blood is characterized by greater electrical conductivity than other tissues and therefore the resistivity of a given limb segment can be considered an indirect measure of its perfusion (Graham, 1996). The test was conducted in a quiet room after a 5-min rest in a supine position. In line with the manufacturer's recommendations, electrodes were placed onto patients' forearms. Mean values of the following parameters were analyzed: (1) impedance ratio (IR) — the ratio of wave amplitude to basic impedance, (2) slope ratio (SR) — the ratio of the maximum slope to basic impedance, (3) crest time (CT) — delay between the point of slope increase and maximum point of the curve, (4) crest width (CW) — the delay between the points at either sides of the curve at the level corresponding to 95% of the amplitude, (5) propagation time (PT) — the delay between the onset of the electrographic R-wave and the beginning of the rheographic wave slope recorded from the patient's forearm, (6) alternating blood flow (ABF) — the amount of blood pumped through the examined body part during the cardiac cycle. All measurements were taken with a RheoScreen Compact device (Medis GmbH).

### 2.4. Applanation tonometry.

The parameters of peripheral pulse were determined with a SphygmoCor CVMS-CPVH device (AtCor Medical). It is an automated device for the examination of central arterial pressure and propagation time based on a peripheral pulse wave recorded by an applanation tonometer. The examinations were conducted in a quiet room after a 5-min rest in a supine position. The detector was placed over the right radial artery at the level of patient's wrist. The results were considered acceptable whenever the data quality index (operator index) was at least 80. After analysis of the wave, the values of peak T1 (wave peak) and peak T2 (peak of the arterial reflection wave) were calculated with dedicated software, and then peripheral augmentation indices were determined from the following formulas: AP/PP and P2/P1, where AP = P2 − P1 / SBP − DBP.

### 2.5. Statistical analysis

Statistical calculations were carried out with Statistica 10 software. Statistical characteristics of the analyzed variables for the study groups were presented as means ± standard deviations, medians (interquartile ranges) or numbers (percentages). Normal distribution of the analyzed variables was verified with the Kolmogorov-Smirnov test and homogeneity of their variances with Levene's test. The significance of intergroup differences was examined with the Student *t*-test or Mann-Whitney *U* test, and with the Pearson chi-square test. The significance of intergroup differences in mean thermographic parameters was verified with covariance analysis (ANCOVA) after adjustment for actual environmental temperature. Correlations between pairs of normally distributed variables were analyzed with Pearson's test, and associations between variables with distributions other than normal with Spearman's test. The results were considered significant at $P < 0.05$.

The minimum sample size providing ≥0.9 statistical power for ≥1 °C difference in digit skin temperature and differences in pulse amplitude was estimated at 45 ET patients and 30 controls.

## 3. Results

### 3.1. Thermography

ET patients showed a tendency to slightly higher metacarpal skin temperatures than the controls (32.97 ± 0.26 vs. 32.52 ± 0.29 °C, $P = 0.302$). Third digit skin temperature in patients with ET was significantly lower than in the controls (31.04 ± 0.41 vs. 32.45 ± 0.46 °C, $P = 0.045$). Evident intergroup differences were found for the temperature gradient (the difference between metacarpus and 3rd finger skin temperature) and subjects with ET presented significantly higher values of this parameter than the controls (1.82 vs. 0.11 °C, $P = 0.000$).

The temperature gradient was not associated with patient age, sex, cigarette smoking, treatment or actual platelet count. Metacarpal skin temperature turned out to be equal or lower than the 3rd finger skin temperature in only two (5.88%) ET patients and 94.12% of the controls (chi$^2$, $P = 0.000$).

In nearly all patients with ET and abnormal thermograms, the metacarpus-3rd finger temperature interface corresponded to the proximal interphalangeal joint (Fig. 1).