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Original Article

Peripheral microcirculatory hemodynamic changes in patients with myocardial ischemia

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Background: Patients with coronary heart disease demonstrate changes in skin microcirculation and a decrease in cutaneous blood mass.
Objective: The goal of this study was to assess the feasibility of diagnosing myocardial ischemia based on peripheral microcirculatory variables.
Methods: The skin microcirculatory measurements were monitored using an LPT system comprising a Laser Doppler Flowmeter (LDF), a photoplethysmograph (PPG) and a transcutaneous oxygen tension device (tc-PO_2). Concurrently, heart rate and blood pressure were monitored. Measurements were performed before and after exercise stress test. Subjects were divided into ischemic (20) and nonischemic (27) patients based on myocardial perfusion imaging (MPI).
Results: The results indicate differences in LPT variables between ischemic and nonischemic patients following exercise, while no differences in the central variable values were observed between the two groups.
Conclusions: Peripheral microcirculatory variables may be useful for non-invasive assessment of myocardial ischemia. The system has clinical potential for sensitive and noninvasive monitoring of vital variables during medical procedures in clinics, as well as in home care for patients who suffer from ischemic cardiac diseases.

1. Introduction

The development of new Cutaneous Blood Flow (CBF) measuring methods throughout the last decades runs concurrently with our understanding of physiological mechanisms of the microcirculation. CBF and tissue oxygenation measurements play an important role in evaluating various conditions such as vasospasm, ischemia, injury and recovery processes and cutaneous implant function [1,2]. The ability to monitor non-invasively changes in the skin microcirculation level leads to improvements both in diagnosis and treatment of patients [3–7].

It was already shown that patients with coronary heart disease demonstrate changes in cutaneous microcirculation and a decrease in cutaneous blood mass [3,8–11]. One of the suggested predictors of risk for cardiovascular disease is Endothelial Function which is based on sensitivity to long-acting nitrates and vasoactive drugs. Studies have suggested that the noninvasive assessment of endothelial function may provide important information for individual patient risk, progress, and guidance of therapy [12–18]. Therefore, there is a need to develop reliable non-invasive tools for assessment of myocardial ischemia, based on peripheral microcirculatory variables.

At the Neufeld Cardiac Research Institute, our group has designed a combined noninvasive system that measures hemodynamic changes in the peripheral microcirculation (LPT system).

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The LPT system consists of LDF, PPG and tc-PO_2 devices that measure the flux of RBC, the amount of RBC, and oxygen tension, respectively. Based on the results of our previous studies, the LPT system can be used as a reliable noninvasive monitor of microcirculatory hemodynamic variables under different clinical conditions such as hemorrhage followed by fluid transfusion [19], different nitrates and vasoactive drugs at different dosages [20] and different respiration rates [21] and during varying degrees of hypoxia [22].

The goal of this study was to assess the feasibility of diagnosing myocardial ischemia based on peripheral microcirculatory variables, using the LPT system.

2. Methods

2.1. Study population and test conditions

The study included 47 subjects (41 males; 6 females; age range 36–75 years; mean age 54.25 years) referred for exercise SPECT imaging. All patients were able to exercise on a treadmill and were instructed to fast for 3 h prior to the test. Patients on vasoactive drugs were instructed to stop taking short-acting nitrates for 6 h, long-acting nitrates and calcium channel blockers for 24 h and beta-blockers for at least 48 h prior to the test. Patients unable to reach at least 85% of the maximal predicted HR, and patients with cutaneous disease at the area of the arm, where the LPT measurements were to be performed, were excluded from the study.

After the blind-test measurements the patients were divided into two groups according to their SPECT imaging results: normal SPECT imaging including negative scans for ischemia, apparently normal and normal scans (Group 1); and abnormal SPECT imaging including mildly positive, positive and severely positive scans for ischemia (Group 2). The study was approved by the Helsinki committee of the Sheba Medical Center, Tel Hashomer, Israel. The patients signed an informed consent following a full explanation of the study purpose.

2.2. Variables measured

Peripheral microcirculatory variables were measured using the LPT system. Since measurement devices are sensitive to motion, it is technically not feasible to measure peripheral microcirculatory variables during exercise because the signal is unstable. Measurements were therefore performed immediately after exercise. The following skin microcirculatory variables were monitored and recorded during the experiment by probes placed on the subject's arm:

Flux of RBC was measured by LDF using a Periflux model PF3 Laser Doppler Flowmeter (Perimed, Sweden). This is a relative measurement and the signal is expressed as perfusion units.

The amount of RBC was measured by PPG, using an EC-5R plethysmograph (D.E. Hokanson Inc.). This is a relative measurement expressed in volts. The instrument was set at AC current, 2 KHz/cm.

Tissue oxygen tension was measured by tc-PO_2, model TCM3 (Radiometer, Copenhagen, Denmark). The heating element was set at 43 °C, providing efficient oxygen diffusion and optimal capillary blood flow [23,24]. The measurement is quantitative and is expressed in mmHg units. It should be noted that any vasodilation due to the local heating effect of the tc-PO_2 probe was eliminated by the comparison between the groups.

Central variables, HR, SBP and DBP, were measured during exercise treadmill tests conducted in a thermally controlled environment of 22–24 °C with humidity lower than 60%. The patients acclimated for 10 min before the measurements were taken. The treadmill exercise test was performed according to the Bruce protocol [25]. Modified 12-lead electrocardiograms (ECG) were recorded at rest, following every 3 min of exercise, at peak exercise and at every minute of the 5-min recovery period. Blood pressure was measured at rest, every 3 min during exercise, and 3 min after the end of exercise. At peak exercise, Tl-201 (3 mCi) was injected intravenously and the patients were asked to continue exercising for one more minute.

Myocardial perfusion imaging, SPECT, was performed approximately 10 min after Tl-201 injection and after 3–5 h of rest. In the presence of a non-reversible or partially reversible defect, a third imaging was performed 18–24 h after the stress [26]. The SPECT studies were visually assessed by two experienced nuclear cardiologists who were blinded to the clinical and LPT data.

2.3. Data processing

Microcirculatory variables are expressed as percent of signals during the rest stage since the PPG and LDF are relative measurements. The measurements were conducted as a "blind test". Subjects' codes were opened only at the data processing stage.

1. Each patient was evaluated according to his microcirculatory and central variables at all stages. Data are expressed as percent of signal since these are relative measurements.
2. Based on SPECT results, patients were divided into non-ischemic (Group 1) and ischemic (Group 2) groups.
3. The SPECT and central variables results were compared with the peripheral microcirculatory results.

Since the peripheral variable results were continuous, an average of 5 results per minute for each measurement stage was performed during time (at rest (*Rest*), immediately after exercise (*Ex*) and after 4 min of recovery (*Rec*)). The systemic variables were measured and monitored at each stage using a computer. All variables are calculated as percentage of the values measured at rest prior to exercise (baseline). In order to correlate between the different variables throughout the experiments, the changes from one stage to another are presented as differences between consequent stages (Eq. (1)).

$$\begin{aligned} D_{Ex-Rest} &= \frac{Ex - Rest}{Rest} \times 100\% \\ D_{Rec-Ex} &= \frac{Rec - Ex}{Rest} \times 100\% \\ D_{Rec-Rest} &= \frac{Rec - Rest}{Rest} \times 100\% \end{aligned} \tag{1}$$

2.4. Statistical analysis

ANOVA (Analysis of Variance) was used for continuous variable analysis to evaluate the change in time of circulatory variables, blood pressure and HR. *t*-Test was used to evaluate statistical significance of the results. Statistical significance was defined when $p < 0.05$.

3. Results

After the complete set of measurements, the patients were divided blindly into two groups according to their SPECT results: Group 1: non-ischemic SPECT included 27 patients (57.4%, 22 males) with an age range of 36–75 years (mean age = 53 years) and Group 2: ischemic SPECT included 20 patients (42.6%, 19 males) with an age range of 41–69 years (mean age = 56 years). Although the average age of Group 1 was lower than that of Group 2, the difference was not statistically significant ($p > 0.05$), and thus age had no influence on the results.