Atherosclerosis 270 (2018) 139–145

Contents lists available at ScienceDirect

Atherosclerosis

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

Vasodilator response to galvanic current stimulation of the skin accurately detects acetylsalicylic acid intake: A study in 400 vascular patients

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ARTICLE INFO

Article history:
Received 27 September 2017
Received in revised form
19 December 2017
Accepted 24 January 2018

Keywords:
Laser speckle contrast imaging
Microcirculation
Peripheral vascular disease

ABSTRACT

Background and aims: The first cause of low-dose acetylsalicylic-acid (ASA) inefficacy is poor adherence to treatment. No non-invasive technique is available to assess ASA intake. Current-induced vasodilation (CIV) was found abolished in healthy volunteers after low-dose ASA intake. We tested clinical characteristics, treatments, and comorbid conditions influencing CIV amplitude in vascular patients.
Methods: CIV was tested in 400 patients (277 males and 123 females, aged 65.4 ± 13.4 years). We focused on clinical characteristics, treatments, and comorbid conditions as covariates of CIV amplitude. We studied the CIV amplitude to covariate relationships with multivariate linear regression and receiver operating characteristics (ROC).
Results: The multivariate linear model determined that ASA intake within the last 48 h and the interaction between ASA intake and body mass index (BMI) were the sole covariates associated with CIV amplitude. For the whole population, the area under the ROC curve (AUC) for CIV to predict ASA intake was 0.853 [95% confidence interval (CI): 0.814–0.892]. Considering separately the areas observed for non-obese (BMI ≤30, n = 303) and obese (BMI>30, n = 93) patients, the AUC [95% CI] was 0.873 [0.832–0.915] and 0.776 [0.675–0.878], respectively ($p = 0.083$).
Conclusions: ASA is the only drug that affects the amplitude of CIV response observed after galvanic current application to the skin of vascular patients. CIV depends on BMI but not age or gender. As such, CIV appears to be a potential objective marker of ASA intake and could facilitate future non-invasive assessments of adherence to ASA treatment.

1. Introduction

Cardiovascular disease resulting from atherosclerosis is one of the leading causes of morbidity and mortality. Antiplatelet agents, unless contraindicated, are systematically prescribed in patients with atherosclerotic disease. Acetylsalicylic acid (ASA), at a dosage of 75–325 mg per day, is the cheapest and one of the most widely used antiplatelet drugs. Worldwide ASA use is estimated to be approximately 120 billion ASA tablets yearly [1]. ASA, even at a low dose, irreversibly blocks platelet cyclooxygenase-I (Cox-I) and thereby inhibits the aggregation of a platelet throughout its lifespan (approximately 8 days) [2]. The efficacy of low-dose ASA to prevent cardiovascular complications has been extensively documented, but 19% of patients treated daily with 100 mg [3] and 40% of diabetic and non-diabetic patients [4] show high on-ASA residual platelet reactivity. The mechanisms underlying the variable response to ASA treatment may be due to biological disorders, inflammation, or accelerated platelet turnover [5]. Nevertheless, it has been suggested that

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https://doi.org/10.1016/j.atherosclerosis.2018.01.041
0021-9150/

most of the patients with high on-ASA residual platelet reactivity do not take their drug regularly [6], which can be the cause of potentially serious thrombotic complications [7]. Beyond patient history, an objective, simple, non-invasive tool that could easily confirm ASA intake and then exclude non-adherence to treatment as a potential cause of ASA inefficacy could be of clinical interest.

In healthy subjects, we previously showed that monopolar galvanic currents of very low intensities elicited a vasodilator response [8] that was completely abolished after low (75 mg) and high (1000 mg) doses of ASA, and remained attenuated for 5 days [9]. Anti-cyclooxygenase-2 (COX2) drugs or inhibitors of the ADP receptor did not modify this Current-induced Vasodilation (CIV), whereas indomethacin (a nonsteroidal anti-inflammatory drug) blocked the CIV response [10–12]. The aim of the present study was to determine whether CIV could be used to test ASA intake in vascular patients to objectively confirm adherence to treatment. Since the influence of other drugs, clinical characteristics, or comorbid conditions on CIV in a large group of adult patients is not known, the objectives of this study were, therefore: first to analyse prospectively the factors eventually impairing CIV, and second to determine the performance of CIV to assess ASA intake and the threshold value to use for objectifying ASA intake.

2. Patients and methods

2.1. Study population

The study was performed among all the patients who were referred for ultrasound vascular arterial evaluation in the University Hospital of Angers. As a routine, patients were asked on arrival to complete a questionnaire on their medical or surgical history, including ongoing medications. Then, patients were admitted to the ultrasound room, and eligibility and inclusion/exclusion criteria were verified. Inclusion criteria were: Caucasian, ability to understand the study goals, and affiliation to the national security insurance system. Exclusion criteria were: pregnancy, exclusion from another biomedical study, refusal or inability to sign informed consent, and protection by law or justice decision.

From January 4 to April 10, 2017, all eligible patients (approximately n = 500) were proposed to participate in the First-Aspirin misuse objective screening (AMOS) study. This study received local ethics committee approval and conforms to the Declaration of Helsinki. It was registered in the American National Institutes of Health database, clinicaltrial.gov, under reference NCT02997436 prior to first inclusion.

Subjects willing to participate gave individual written, informed consent. Self-completed questionnaires were checked for completion and finished, if required. Data collected for the study included 8 clinical items: age, gender, weight and stature (to calculate body mass index (BMI)), active smoking, hypertension, hypercholesterolaemia, and diabetes mellitus. We also recorded ongoing treatment from the patient's history and data file, including ASA intake within the last 48 h. Drugs other than ASA were classified into 13 categories: cholesterol-lowering drugs (e.g., cholesterol absorption inhibitors, statins, fibrates); beta-blockers; inhibitors of the renin angiotensin system (e.g., angiotensin II receptor antagonists, angiotensin converting enzyme inhibitors, inhibitors of renin); diuretics; alpha-blockers; calcium channel blockers; anticoagulants (e.g., vitamin K inhibitors, thrombin inhibitors, Factor X inhibitors, heparin); antiplatelet agents (e.g., ADP inhibitors; ATP analogues); antidiabetic drugs (e.g., biguanides, insulin; antidiabetic sulphonamides, glinides, glucagon-like peptide 1 (GLP-1) analogues, gliptins); corticosteroids; nonsteroidal anti-inflammatory drugs; neuropsychiatric drugs (e.g., antidepressants, benzodiazepines, immunosuppressors/modulators, anticonvulsive drugs); and other categories (e.g., antiarrhythmic drugs, proton pump inhibitors, thyroid hormones, vitamins).

Thereafter, included patients were instructed to lie comfortably in a semi-supine position for the microvascular test. Microvascular experiments were performed in a specific, air-conditioned room (23 ± 1 °C), with low lighting conditions.

2.2. Preparation of subjects and recordings

For microvascular recordings, we studied cutaneous blood flow (CBF) on the unshaved volar aspect of the forearm, using Laser speckle contrast imaging (LSCI). We used a specifically designed transparent electrodes that allows simultaneous CBF recording and current application: referred to as the “active electrodes”, (probe LI611, Perimed AB, Järfälla, Sweden). These “active” probes have a circular, 0.2 mL transparent chamber of ~1 cm^2 that is filled with deionized water and connected to a regulated current supply (Perilont Microphamacology System PF 382, Perimed AB). The other lead of the current supply was fixed to a disposable adhesive PF384 dispersive electrode (Perimed AB) that was positioned 5 cm away from the active electrode, closing the circuit.

A 4-cm^2 opaque bilayer adhesive (OBA) patch was fixed on the subject's right forearm. This OBA patch is made of Comfeel® and aluminium and was previously validated to automatically reduce noise in the LSCI signal from movement artefacts [13].

LSCI recordings were made using a 70-mW system (PeriCam PSI System®, Perimed AB) at a sampling rate of 5 Hz. The distance between the laser head and skin was set to 15 cm.

A first period of LSCI recording of the forearm was carried out for 30 s before current delivery (T-0). Then, CIV was performed by two consecutive, 5-s pulses of 0.10 mA cathodal application, separated by an interval of 4 min. A second period of LSCI recording was started ~10 min after the end of the second current pulse (T-14) and again performed for 30 s. Images were stored on a computer for offline analysis.

2.3. Image analysis

Recordings were analysed offline by investigators, blinded to the results of the questionnaires. Regions of interest (ROI) of approximately 0.60–0.75 cm^2 were defined by the observer on the initial image of the forearm. One ROI was in the middle of the transparent active probe (ROI-1), one was on the skin (ROI-2), and one was on the OBA patch (ROI-3). The mean LSCI values were calculated over 20 s of recording, avoiding the first and last 5 s of each recorded period.

The signal amplitudes backscattered from the various ROIs at T-0 and T-14 were automatically calculated using the manufacturer's software (PimSoft® 1.2.2.0; Perimed AB). From recorded images, the ROIs could be manually moved and recentred if ample movements resulted in them no longer being in the areas of interest. The PimSoft® software expresses recorded values in arbitrary perfusion units (LSPU); raw data were exported to an Excel spreadsheet (Excel 2002 V3®, Microsoft, USA).

2.4. Data processing

We calculated the change in CBF from ROI-1 and ROI-2 between T-14 and T-0. Thereafter, ROI-2 changes were subtracted from ROI-1 changes in order to account for eventual changes in systemic conditions. The OBA patch was only used here for quality control and not for reducing noise from the LSCI signal, contrary to our