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Discrimination between different degrees of coronary artery disease using time-domain features of the finger photoplethysmogram in response to reactive hyperemia

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ABSTRACT

Atherosclerosis is a major cause of coronary artery disease leading to morbidity and mortality worldwide. Currently, coronary angiography is considered to be the most accurate technique to diagnose coronary artery disease (CAD). However, this technique is an invasive and expensive procedure with risks of serious complications. Since the symptoms of CAD are not noticed until advanced stages of the disease, early and effective diagnosis of CAD is considered a pertinent measure.

In this paper, a non-invasive optical signal, the finger photoplethysmogram (PPG) obtained before and after reactive hyperemia is investigated to discriminate between subjects with different CAD conditions. To this end, the PPG from both index fingers and standard 3-lead ECG of 48 patients (16 females, age 54.3 ± 9.6 years and 32 males, age 59.9 ± 10.6 years) scheduled for diagnostic angiography were recorded. The coronary condition of each subject was determined by three expert cardiologists (ground truth) based on these coronary angiograms. Of the 48 patients, 18 were diagnosed as having no disease (normal coronary – NC), 3 were diagnosed as having mild stenosis (MLD), 11 had single-vessel disease (SVD), 5 had two-vessel disease (2VD) and the remaining 11 were reported to have three-vessel disease (3VD). A vessel disease was determined when a significant (more than 50%) stenosis of the lumen cross-sectional area was observed. The 48 subjects were first grouped into two classes, namely high-risk: Class 1 = {2VD, 3VD} ($N = 16$) and low-risk: Class 2 = {NC, Mild, SVD} ($N = 32$). Using this approach, classification using a k-Nearest Neighbor classifier leads to an accuracy of 81.5%, a sensitivity of 82.0% and a specificity of 80.9%. Then all 48 subjects were regrouped slightly differently by moving the SVD subjects from the second (low-risk) to the first (high-risk) class. Therefore for the second approach high-risk: Class 1 = {SVD, 2VD, 3VD} ($N = 27$), whereas low-risk: Class 2 = {NC, Mild} ($N = 21$). This second approach resulted in an accuracy of 78.8%, a sensitivity of 79.3% and a specificity of 78.3%. We submit that this technique can be employed to implement an efficient triage system for scheduling coronary angiography, as it is able to identify non-invasively patients at greater risk of coronary stenosis.

Abbreviations: 2VD, two-vessel disease; 3VD, three-vessel disease; AC, amplitude; ACC, accuracy; CAD, coronary artery disease; CE-MARC, clinical evaluation of magnetic resonance imaging in coronary heart disease; CMR, cardiac magnetic resonance; CT, computed tomography; CTm, crest time; ECG, electrocardiography; ED, endothelial dysfunction; FMD, flow-mediated dilation; HDL, high density lipoprotein; HR, heart rate; IVUS, intravascular ultrasound; k-NN, k-Nearest Neighbor; LDL, low density lipoprotein; MLD, minimum lumen diameter; MRI, magnetic resonance imaging; MSCT, multi-slice computed tomography; NC, normal coronary; NPV, negative predictive value; PPG, photoplethysmogram; PPV, positive predictive value; PTT, pulse transit time; RV, rising velocity; Sn, sensitivity; Sp, specificity; SPECT, single photon emission computed tomography; SV, stroke volume; SVD, single-vessel disease; TG, triglyceride; TME, treadmill echocardiography; UBE, upright bicycle echocardiography; US, ultrasound.

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1. Background

1.1. CAD and endothelial dysfunction

Accumulation of atheromatous plaques made up of cholesterol-laden fatty streak within the walls of the coronary arteries is the major cause of coronary artery disease (CAD) [1]. Atherosclerosis, the subsequent thickening and hardening of the coronary artery walls, is considered as the main cause of CAD [2]. The deposition of plaque in the arteries limits blood flow to the cardiac muscle, leading to myocardial infarction and heart attack. CAD has been identified as one of the leading causes of morbidity and mortality worldwide whereas ischemic heart disease has been the first cause of death throughout the world in 2012 [3]. In the European Union alone, CAD burden was estimated to over €60 billion in 2009 [4].

Several tests do exist for CAD diagnosis: coronary angiography, intravascular ultrasound (IVUS) and exercise electrocardiography (ECG) [1]. Although considered as the gold standard for detecting CAD, coronary angiography is an invasive method with considerable risk, from one to two per thousand [5]. Intravascular ultrasound (IVUS) can be employed with a reported accuracy of 61%, sensitivity of 53% and specificity of 69% in discriminating between subjects with and without coronary stenosis [1]. Depending on the protocol, exercise ECG has a sensitivity of 25–71% for patients with one artery occlusion [1]. In patients with two or three artery occlusions, exercise ECG is reported to have a sensitivity of 81% and a specificity of 66% [1]. The main challenge is the difficulty in finding the right balance between accuracy, safety and convenience for the patient and financial aspects of the proposed screening tests.

A comparative study was conducted on symptomatic patients with stable angina who were referred for noninvasive stress testing (exercise bicycle test and/or single photon emission computed tomography (SPECT)) and invasive coronary angiography; all patients underwent additional 64-slice CT coronary angiography. In this study, SPECT and CT coronary angiography yielded a high diagnostic performance (sensitivity 89% and 98%; specificity 77% and 82%) which was superior to exercise bicycle testing (sensitivity 76%, specificity 47%) [6].

In another study [7], the performance of two exercise stress echocardiography methods i.e. the conventional post-treadmill echo (post-TME with Bruce protocol) and peak upright bicycle echo (peak-UBE) were investigated in 86 patients referred for coronary angiography with suspected or known CAD. It is shown that peak-UBE has a better sensitivity than post-TME (88% vs. 66%) with similar specificity of 89%. However, a recent meta-analysis of 226 studies [8] shows that for stress echocardiography (including studies using exercise or pharmacologic stress), in general a sensitivity of 79% and specificity of 87% are achieved.

In the CE-MARC study [9], three diagnostic tests including coronary angiography, SPECT and cardiac magnetic resonance imaging (CMR) are conducted on a prospective population with a CAD prevalence of 39%. The results show that CMR has greater sensitivity (86.5% vs. 66.5%) and *NPV* (90.5% vs. 79.1%) than SPECT for diagnosis of significant CAD, although the sensitivity of SPECT in the mentioned study is considerably lower than the sensitivity of 85% reported by other meta-analysis studies [10,11].

The performance of multi-slice computed tomography in CAD diagnosis is evaluated using a state-of-the-art 320-slice multi-slice CT device [12]. The diagnostic performance of CT coronary angiography can be considerable (sensitivity of 96% and specificity of 88% [13]) especially using modern multi-detector devices. However, this performance is negatively affected in patients with high calcification score (i.e. Agaston calcium score > 600) [14]. Therefore, calcium score pre-test is needed before CT angiography to avoid unnecessary radiation exposure.

Since the symptoms of the disease are noticed only at an advanced state, CAD screening can be a crucial averting measure. It is known that the function and the structure of vessels are impaired well before any observation of cardiovascular disease (CVD) symptoms becomes apparent [15]. More specifically, endothelial dysfunction (ED) is considered as one of the primary reasons for artery sclerosis and ischemic heart disease [16], and it has been found to be closely ($p < 0.05$) associated with cardiovascular events [17,18]. Thus, the study of ED may be considered as one of the methods to indirectly establish a basis for risk stratification of CAD [16].

1.2. Endothelial dysfunction assessment techniques

A key quantifiable feature of ED is the inability to release vasodilators (i.e. nitric oxide), resulting in the poor dilatation response of the vessel wall to a physical or chemical stimulus [19]. Among the earliest attempts to assess endothelial dysfunction was the work of Ludmer et al. utilizing intracoronary infusion of acetylcholine and quantitative coronary angiography [20]. Though considered the gold standard [21], direct assessment of ED in coronary arteries is an invasive method that can just be recommended for those patients undergoing coronary angiography. This limitation led the researchers to try to find noninvasive methods or surrogate sites in the vascular system for the evaluation of ED. Due to its relatively ease of accessibility and based on the seminal work of Celermajer [22], the most widely used anatomical site in non-invasive tests for evaluating the endothelial dysfunction is the brachial artery. It has been shown that the endothelial function in brachial and coronary arteries is correlated ($r = 0.41$, $p = 0.003$) [23].

To this end, the flow-mediated dilation (FMD) test is employed [22] whereas reactive hyperemia is induced via a temporary artery occlusion. The resultant relative increase in the brachial artery diameter is measured by B-mode ultrasound (US-FMD). Although non-invasive, this technique is considered costly since it requires a high-frequency (>10 MHz) ultrasound imaging instrument being able to produce high-resolution (pixel separation < 100 μm) images. Furthermore, the accuracy of the results depends highly on the skills of the operator [22,24].

An alternative method to US-FMD has been proposed in assessing the endothelial function in the FMD test using the photoplethysmogram signal (PPG) [25–29]. The PPG, as comprehensively studied in [30], represents the volumetric changes in blood vessels and can easily be recorded by a sensor consisting of a light source and a photo detector. The principle of PPG is that light (mainly red, infrared or green) traveling through biological tissues (e.g. the fingertip or earlobe) will be absorbed by different tissues (skin, muscle, fat, bone, arterial and venous blood). Arterioles contain more blood during systole than diastole, as their diameters change due to blood pressure pulses. The detected light reflected from (in reflective mode PPG) or transmitted through (in transmissive mode PPG) the vessels will thus fluctuate synchronously with the pulsatile blood circulation. The advantages of using the PPG include easy setup, simple operation and low cost. It is even possible to record the PPG without any direct contact with the skin surface [31]. The above advantages may explain why PPG technology has attracted much attention in clinical applications [32–36]. Among these, there have been attempts to assess the endothelial function and presence of CAD through PPG signal processing in the FMD test [26,28,29]. The amplitude difference between a systolic peak and corresponding diastolic foot of the PPG (AC) during FMD was utilized for the purpose of diagnosis, and it was shown that the peak PPG-AC is reached significantly faster than the peak FMD measured by ultrasound ($p < 0.001$) [29].