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Short Communication

The waveform index of the ophthalmic artery predicts impaired coronary flow reserve☆,☆☆

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ABSTRACT

Background: Coronary flow reserve (CFR) can decrease with impairment in coronary microcirculation, even in the absence of epicardial conduit obstruction. Recently, the ophthalmic artery (OA), which is the first major branch of the internal carotid artery and is representative of microarterioles, has been identified using color Doppler sonography. However, the features of ultrasound waveform indices suggestive of impaired OA microcirculation and the relationships between these indices and CFR have not been elucidated. The present study aimed to assess the features of ultrasound waveform indices suggestive of impaired OA microcirculation and the relationships between these indices and CFR.

Methods and results: A total of 30 consecutive patients with a normal coronary angiogram and normal left ventricular function were studied. Patients with ≥25% stenosis of the right common or internal carotid artery were excluded. The CFR was defined as the ratio of adenosine-induced hyperemic to baseline blood flow velocity with an intracoronary Doppler guidewire. Color Doppler imaging was used to determine the blood flow velocity of the right OA, and the indices of peripheral resistance (resistance index [RI], pulsatility index [PI], and systolic mean velocity to diastolic mean velocity [Sm/Dm] ratio) were calculated. The ultrasound form showed a distinctive biphasic wave during systole followed by a monophasic wave during diastole. The velocity component in the early-systolic wave was higher than that in the mid-systolic wave or the diastolic wave (31.4 ± 5.1 vs. 26.1 ± 5.4 vs. 15.9 ± 4.0 cm/s, $P < 0.0001$). The RI and PI were not related to the CFR, and the Sm/Dm ratio was negatively correlated with the CFR ($\beta = -0.415$, $P = 0.022$). However, the relationship was attenuated by clinical variables closely associated with the Sm/Dm ratio or CFR, and hemoglobin A1c was a common mediator. The best Sm/Dm ratio cutoff for predicting an impaired CFR was 2.5 based on a receiver operating characteristic curve analysis.

Conclusions: An increase in the Sm/Dm ratio, which reflects a characteristic waveform, indicates impaired OA microcirculation. The ratio is negatively correlated with CFR, and therefore, it may be applied for the noninvasive evaluation of coronary physiology. Furthermore, hemoglobin A1c may be a common mediator for the OA and coronary microcirculation.

Introduction

The role of microcirculatory dysfunction in various organs has been of increasing interest. The diameter of the epicardial coronary arteries detected by coronary angiography ranges from approximately 500 μm to 5 mm, whereas coronary microvascular dysfunction is defined as disordered function of small coronary resistance vessels <100–200 μm in diameter (Hozumi et al., 1998; Camici and Crea, 2007). In the absence of epicardial coronary artery stenosis, coronary flow reserve (CFR) may be impaired due to coronary microvascular dysfunction (Camici and Crea, 2007). The ophthalmic artery (OA) is the first major branch of the internal carotid artery and its diameter is estimated to be <2 mm (Erdogmus and Govsa, 2007; Jimenez-Castellanos et al., 1995; Perrini et al., 2007). The central retinal artery, which is a major branch of the OA, penetrates into the optic nerve and supplies blood to the retina. Changes in OA blood flow have provided new insights into various vascular disorders, and the Doppler flow pattern of the OA is associated with severity in patients with diabetic retinopathy (Mendivil et al., 1995; Paivansalo et al., 2004; Ino-ue et al., 2000). Because the ophthalmic and coronary arteries are terminal arteries, their impaired microcirculation, as revealed by microangiopathy, may explain malfunction in dominated lesions. Therefore, we hypothesized that OA ultrasound waveforms are affected by traditional cardiovascular risk factors and

Abbreviations: CFR, coronary flow reserve; CAD, coronary artery disease; Dm, diastolic mean velocity; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; OA, ophthalmic artery; PCWP, pulmonary capillary wedge pressure; PI, pulsatility index; RI, resistive index; Sm, systolic mean velocity.

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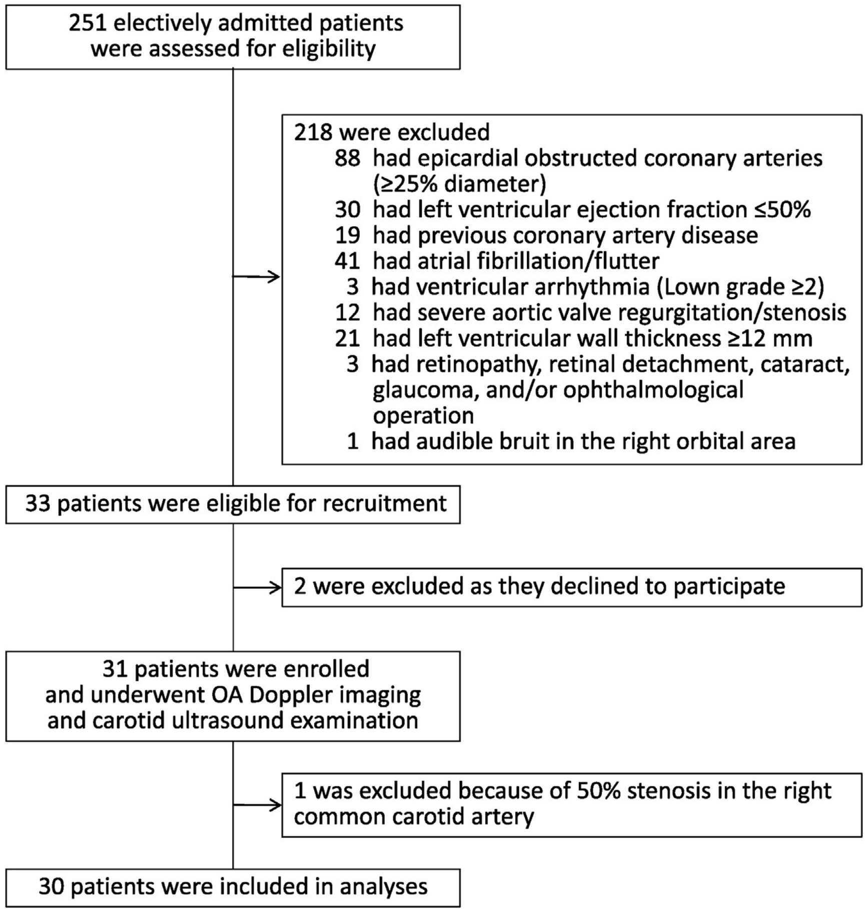

Fig. 1. Flow chart of the recruitment of the study patients with angina-like symptoms OA: ophthalmic artery.

that there is a relationship between these indices and CFR in patients without obstructed coronary and carotid arteries, and we aimed to confirm these hypotheses in the present study.

Material and methods

Study population, coronary angiography, and CFR measurements

We enrolled electively admitted patients with angina-like symptoms, epicardial unobstructed coronary arteries, and normal left ventricular contraction confirmed by diagnostic catheterization at Kumamoto University Hospital. Coronary risk factors were hypertension (>140/90 mm Hg or taking antihypertensive medications), diabetes mellitus (symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dL, fasting plasma glucose concentration ≥126 mg/dL, 2-h plasma glucose concentration ≥200 mg/dL during 75 g oral glucose tolerance test, or taking medications for diabetes mellitus), dyslipidemia (high-density lipoprotein cholesterol <40 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, or triglycerides ≥150 mg/dL or taking medications for dyslipidemia), and current smoking (smoking within the last 1 year). Exclusion criteria were epicardial obstructed coronary arteries (≥25% diameter); left ventricular ejection fraction ≤50%; previous coronary artery disease; atrial fibrillation/flutter; ventricular arrhythmia (Lown grade ≥2); severe aortic valve regurgitation or stenosis; left ventricular wall thickness >12 mm; retinopathy, retinal detachment, cataract, glaucoma, and/or ophthalmological operation; and the presence of audible bruits in the orbital area. Additionally, patients with ≥25% stenosis in the common or internal carotid artery were excluded. All included patients underwent coronary angiography. CFR measurements using an intracoronary Doppler guidewire under basal conditions and during maximal hyperemia were performed in the left anterior descending artery. Impaired CFR was defined as a reserve of <2.5. Written informed consent was obtained from each patient, and the present study was approved by the ethics committee of Kumamoto University. The investigation also conformed to the principles outlined in the Declaration of Helsinki.

Evaluation of OA blood flow velocity and the carotid artery

Right-sided OA Doppler imaging, using the method of Lieb et al. (1991), and right carotid ultrasound examination were simultaneously performed by the same operator blinded to the patients' clinical characteristics. An ultrasound unit (SONOS 5500, Philips, Amsterdam, The Netherlands) with a 1–3-MHz transducer for OA Doppler imaging and a 7.5 MHz transducer for carotid ultrasound was used in this study. Details of the identification of the OA and a schema of the OA Doppler waveform have been presented elsewhere (Maruyoshi et al., 2010). Pulsed Doppler spectral analysis of the OA revealed the peak systolic velocity, end-diastolic velocity, mean systolic velocity (Sm), mean diastolic velocity (Dm), and mean total velocity. The resistance index (RI) and pulsatility index (PI) were calculated as follows: RI = ([peak systolic velocity − end-diastolic velocity]/peak systolic velocity); and PI = ([peak systolic velocity − end-diastolic velocity]/mean total velocity). To evaluate OA hemodynamics, we also calculated the ratio of systolic to diastolic mean velocity (Sm/Dm).

Statistical analysis

All values are presented as means ± standard deviations, and categorical variables are expressed as numbers and percentages. Continuous