



Prevalence of coronary macro- and micro-vascular dysfunctions after drug-eluting stent implantation without in-stent restenosis☆



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ARTICLE INFO

Article history:

Received 22 May 2016

Accepted 29 July 2016

Available online 30 July 2016

Keywords:

Microvascular dysfunction

Recurrent event

Drug-eluting stent

Acetylcholine

Coronary vasomotion

ABSTRACT

Background: The aim was to examine the prevalence and characteristics of epicardial vasomotor abnormality (EVA) and coronary microvascular dysfunction (CMD) including endothelium-dependent (EDCMD) or -independent (EICMD) in patients following a second-generation drug-eluting stent (second DES) implantation without in-stent restenosis.

Methods and results: In 105 patients who underwent second DES implantation in the left anterior descending coronary artery (74 men; mean age, 67.9 ± 9.6 years), and in 105 suspected angina patients without stenting (65 men; mean age 66.4 ± 9.1 years), we evaluated EVA using the acetylcholine provocation test, EDCMD and EICMD by measuring the coronary flow reserve and the relationship between myocardial ischemia (intracoronary lactate production between aorta and coronary sinus and ST-T changes) or recurrent angina and vascular function.

There was no difference in the incidence of EVA between DES and control (49.5% versus 55.2%; $P = 0.41$). Given that the prevalence of CMD was higher in DES than in control (59.0% versus 29.5%; $P < 0.001$), CMD may be associated with stent placement. Of the CMD patients, EDCMD alone, EICMD alone, and both CMDs were found in 40.3%, 22.6%, and 37.1%, respectively. Myocardial ischemia was detected in 42.4% of patients, and recurrent angina was more common in the presence of both EDCMD and EICMD in patients with EVA or CMD compared to patients with normal vascular function (EVA, 42.9% versus 7.7%, $P = 0.015$; CMD, 39.1% versus 7.7%, $P = 0.007$).

Conclusions: Myocardial ischemia and recurrent angina may be caused by the presence of both EDCMD and EICMD after a second DES implantation without ISR.

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1. Introduction

Evaluating patients with recurrent chest pain after successful percutaneous coronary intervention (PCI) represents a challenging task for clinical cardiologists [1]. In Japan, follow-up coronary

Abbreviations: ACh, acetylcholine; ACS, acute coronary syndrome; APV, average peak velocity; BMS, bare-metal stent; CAD, coronary artery disease; CAG, coronary angiography; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; DES, drug-eluting stent; EDCMD, endothelium-dependent coronary microvascular dysfunction; EICMD, endothelium-independent coronary microvascular dysfunction; EVA, epicardial vasomotor abnormality; FFR, fractional flow reserve; GTN, glyceryl trinitrate; hMR, hyperemic microvascular resistance; ISR, in-stent restenosis; LAD, left anterior descending; PCI, percutaneous coronary intervention; Pd, mean average distal pressure; QCA, quantitative coronary angiography; STEMI, ST-elevation acute myocardial infarction.

☆ Clinical Trial Registration: This study was registered in the UMIN protocol registration system (identification number UMIN00019245).

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angiography is often performed in search of significant in-stent restenosis (ISR) at about 9 months after stent implantation irrespective of recurrent angina or angina-like chest pain. No significant ISR can be detected in most patients in the era of the drug-eluting stent (DES), which is different from the era of the bare-metal stent (BMS); however, some patients have complaints of chest oppression at rest or during exercise, although they have no ISR. We recently reported a high incidence of provoked coronary spasm by intracoronary injection of acetylcholine in patients with a previous PCI [2]. About half of the patients had an epicardial coronary spasm according to the acetylcholine provocation test; yet, coronary microvascular dysfunction (CMD), which reportedly raises concern about angina or angina-like chest pain, was unclear [3, 4]. Epicardial coronary artery spasm and CMD have been described as potential mechanisms for recurrent exertional or rest angina but without ISR in patients with previous stent implantation [5–7], and this phenomenon about microcirculatory function is specifically termed post-stent “iatrogenic coronary microvascular dysfunction” [8]. However, these findings have not been investigated systematically and thoroughly. In the present study, we evaluated the following in patients

undergoing second-generation (second) DES implantation without ISR: 1) the prevalence of epicardial vasomotor abnormalities (EVA) and CMD after stent placement, 2) the relationship between EVA or CMD and myocardial ischemia despite no ISR, and 3) the relationship between endothelium-dependent (EDCMD) or endothelium-independent coronary microvascular dysfunctions (EICMD) and myocardial ischemia including recurrent angina.

Moreover, we have a 30-year history of studying and reporting the pathophysiology and clinical feature of non-obstructive coronary artery disease, including epicardial and microvascular coronary spasm [2,9–13], thus, to elucidate the relationship between stent placement and EVA or CMD, we used data on suspected angina in stable patients who underwent acetylcholine (ACh) provocation test and were diagnosed with epicardial vascular dysfunction or microvascular coronary artery disease without stenting in our hospital. We also examined the usefulness of physiologic parameters, including hyperemic microvascular resistance (hMR) as an index of microvascular resistance using a dual-sensor (coronary blood velocity and pressure)-equipped guidewire.

2. Methods

2.1. Study subjects

As shown in Fig. 1, we recruited suspected coronary artery disease (CAD) patients between July 2011 and February 2015, and divided them into 2 categories: obstructive CAD and suspected non-obstructive CAD. Obstructive CAD patients underwent PCI with second DES at Kumamoto University Hospital according to the guideline for PCI [14,15]. Suspected non-obstructive CAD patients underwent the intracoronary ACh provocation test and measurements of trans-cardiac lactate production and coronary flow reserve (CFR) and were finally diagnosed with non-obstructed CAD and non-CAD.

With regard to the DES group, we firstly selected patients who underwent a second DES implantation in the left anterior descending (LAD) artery to minimize bias that vasoconstriction is likely to occur in a coronary artery, because there is a difference in the incidence of

coronary spasm among the three major arteries, i.e., the LAD, left circumflex, and right coronary artery. Selection of a second DES was performed as a default strategy, except for ST-elevation acute myocardial infarction (STEMI). The cobalt–chromium everolimus-eluting stent (CoCr-EES, Xience®, Abbott Vascular) and biolimus-eluting stent (BES, Nobori®) were used. The stent choice was random. The number of patients with EES or BES was 64 or 41, respectively.

In the days of enrollment at our hospital, DES implantation for STEMI was not performed because there was no information on the patients' bleeding risk, malignant disease, or anticipated major surgery. During the follow-up period, patients developing emergent adverse cardiovascular events, including acute coronary syndrome (ACS), were excluded. Patients presenting with stable and recurrent angina or without chest symptoms received scheduled coronary angiography at about 9 months after PCI, and among those patients, cases with significant ISR were excluded. Significant ISR was defined by the American Heart Association as >75% stenosis and apparent ischemic findings (by scintigraphy or electrocardiogram) during an exercise or stress test. In addition to the ISR cases, those with uncontrolled arrhythmias; congestive heart failure; resting hypertension >180/110 mm Hg; significant endocrine, hepatic, renal, or inflammatory diseases; and malignant tumors were excluded from the study (others; $n = 23$, in Fig. 1). Finally, as shown in Fig. 1, this study included 105 consecutive patients (74 men and 31 women, mean age 67.9 ± 9.6 years) for the DES group.

Moreover, to clarify the relationship between stent placement and macro- or microvascular dysfunctions, we recruited stable patients with suspected angina but without stent implantation who were admitted to our hospital. We performed the same examination such as ACh provocation test, measurements of trans-cardiac lactate production and coronary blood flow in 105 suspected non-obstructive coronary artery disease patients who were adjusted by age, gender, and coronary risk factors (hypertension and diabetes mellitus) by a propensity score matching method as the control group (65 men; mean age 66.4 ± 9.1 years) (Fig. 1).

The study was conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was in agreement with the guideline of the ethical committee of Kumamoto University (Institutional Review Board of Kumamoto University), and written informed consent was obtained from each patient or the patient's next of kin.

2.2. Acetylcholine provocation test

All patients had coronary vasomotor response to ACh and physiologic parameters measurement. With regard to the DES group, these invasive tests were performed in the follow-up coronary angiography (CAG) at 9 months after DES implantation irrespective of the presence of chest symptoms except for the recurrence of ACS before 9 months,

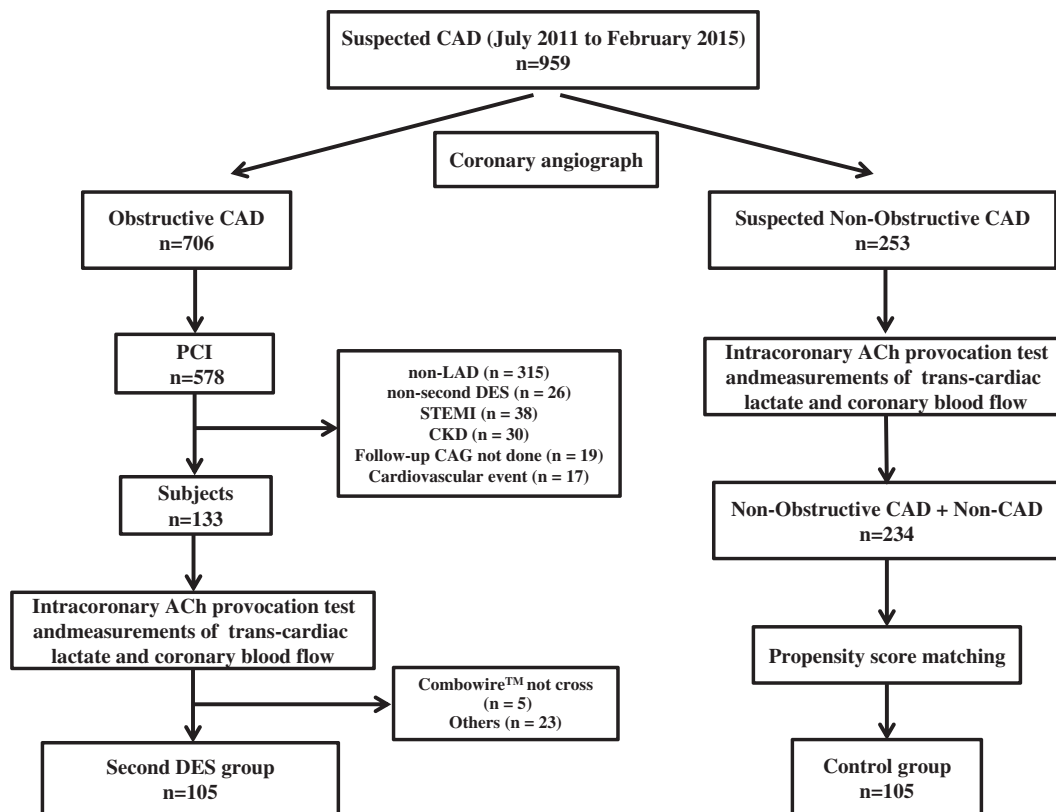


Fig. 1. Flow chart for drug-eluting stent (DES) and control groups in patients with suspected coronary artery disease (CAD). CAD, coronary artery disease; CKD, chronic kidney disease; second DES, second-generation drug-eluting stent; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; STEMI, ST-elevation acute myocardial infarction; CAG, coronary angiography.

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