Journal of Cardiology 71 (2018) 52–58

Contents lists available at ScienceDirect

Journal of Cardiology

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

Original article

Application of pressure-derived myocardial fractional flow reserve in chronic hemodialysis patients

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ARTICLE INFO

Article history:
Received 8 January 2017
Received in revised form 19 May 2017
Accepted 26 May 2017

Keywords:
Coronary artery disease
Fractional flow reserve
Renal disease
Chronic
Imaging
Myocardial perfusion

ABSTRACT

Background: Although fractional flow reserve (FFR) measurements during coronary angiography are performed in routine clinical practice, few studies have evaluated FFR measurements in dialysis patients.
Methods: We retrospectively studied 42 hemodialysis patients with suspected or known coronary artery disease (CAD) who underwent stress myocardial perfusion imaging and coronary angiography with FFR measurements for 61 coronary lesions. The cut-off value for FFR to detect myocardial ischemia was determined by receiver operating characteristic (ROC) curve analysis.
Results: There were 61 coronary vessels measured by FFR. The FFR range was 0.34–0.93 with a mean of 0.74 ± 0.13. The ROC curve analysis revealed that the best cut-off value of FFR for detecting myocardial ischemia was 0.76 ($p < 0.0001$), with 70% sensitivity, 86% specificity, and 76% accuracy for myocardial ischemia. Compared with patients who had positive myocardial ischemia and an FFR $\leq$ 0.76, those who had negative myocardial ischemia despite an FFR $\leq$ 0.76 had less left ventricular (LV) mass index, whereas patients who had positive myocardial ischemia despite an FFR $>$ 0.76 had greater LV mass indexor serum calcium-phosphorus product.
Conclusions: The cut-off value of FFR for myocardial ischemia in chronic hemodialysis patients is similar to that in other CAD patients. However, caution is necessary when FFR measurements are applied to dialysis patients with significantly increased LV mass index or serum calcium-phosphorus product.

Introduction

The use of fractional flow reserve (FFR) to assess the functional severity of coronary artery disease (CAD), in particular for an intermediate coronary stenosis, has become a routine clinical practice [1–3]. Landmark clinical trials have reported that FFR measurement is used not only for diagnosing myocardial ischemia but also for predicting the prognosis of CAD patients. However, theoretical limitations for FFR measurements exist in various conditions such as diabetes mellitus, myocardial infarction (MI), and severe left ventricular hypertrophy (LVH) [4]. Although there have been reports of FFR being used for effectively diagnosing ischemia in patients with diabetes mellitus and prior MI [5,6], there are very few studies suggesting the efficacy of FFR for diagnosing myocardial ischemia in chronic hemodialysis (HD) patients in whom marked LVH is usually observed [7]. For chronic HD patients, comorbidities such as CAD and other vascular diseases are key factors that heavily affect prognosis [8,9]. Therefore, we retrospectively evaluated the plausibility of FFR measurements in chronic HD patients as assessed by stress myocardial perfusion imaging (MPI).

Materials and methods

Study population

Of 307 chronic dialysis patients examined by MPI between April 2001 and July 2015 from 3 institutions, we retrospectively

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http://dx.doi.org/10.1016/j.jjcc.2017.05.007
0914-5087/

analyzed 42 consecutive studies with suspected or known CAD patients who underwent stress MPI and coronary angiography (CAG) with FFR measurements for 61 coronary lesions. Stress MPI was performed within 3 months of cardiac catheterization in all cases. Patients with advanced atrioventricular block, severe LVH caused by, for example, aortic stenosis (AS) or hypertrophic cardiomyopathy, and those after coronary artery bypass graft surgery were excluded [10,11]. We consider a posterior wall thickness of ≥17 mm measured by echocardiogram as severe LVH. We regard an aortic valve area of ≤1.0 cm^2 as AS. There were 23 men and 19 women with an average age of 67 ± 10 years (range, 41–84 years). Hypertension was observed in 40 patients, diabetes mellitus in 32, and dyslipidemia in 18; furthermore, 10 cases had a history of MI. Dyslipidemia is defined by the Japan Atherosclerosis Society Guidelines as follows: low-density lipoprotein ≥140 mg/dl and/or high-density lipoprotein <40 mg/dl and/or triglycerides ≥150 mg/dl, and/or taking lipid-lowering medication [12].

The complete blood cell counts and the serum levels of urea nitrogen, creatinine, calcium, phosphorus, total protein, albumin, and total cholesterol of all the patients were measured. This study was approved by the Ethics Committee of Tokyo Medical University (No. 2853).

Echocardiography

Echocardiography measurements were performed in 41 patients. In each subject, cardiac chamber quantification by 2D echocardiography was performed according to the guidelines provided by the American Society of Echocardiography [13]. Interventricular septal wall thickness and posterior wall thickness at end-diastole, and left ventricular (LV) internal dimension at both end-diastole and end-systole were also measured using 2D images from the parasternal long-axis acoustic window. LV end-diastolic volume and end-systolic volume were measured by the Simpson disk method using 2D images from the apical 4- or 2-chamber views. Ejection fraction was calculated using the standard equation. LV mass was calculated based on the area-length formula as previously described [13], and it was indexed for body surface area when appropriate.

Stress MPI

Using thallium-201 (^{201}Tl), technetium 99m-sestamibi (^{99m}Tc MIBI), or technetium 99m-tetrofosmin (^{99m}Tc TF), stress/rest MPI was performed. The stress protocol was by either exercise [14] or using adenosine triphosphate (ATP) [15,16]. Both methods were routinely used at each institution and the administration method to induce stress was not particularly regulated. Data were acquired with a gamma camera (Prism 2000XP or Prism 3000XP or PRISM IRIX, Picker, Cleveland, OH, USA) and a high-speed cadmium-zinc-telluride (CZT) camera with a pinhole collimator (Discovery NM 530c; GE Healthcare, Haifa, Israel). MPI for a gamma camera was reconstructed from the data with a data processor (Odyssey VP, Picker) combined with a Butterworth filter (order 8; cut-off frequency 0.25 cycles/cm) and a ramp filter. The high-speed CZT camera system is equipped with a multiple-pinhole collimator and 19 stationary CZT detectors that simultaneously focus on the heart to maximize the efficiency of MPI. No scatter or attenuation corrections were made. Each MPI was divided into 17 segments [17]. The accumulation of radioisotopes in the myocardium was visually evaluated by 2 cardiologists who were blinded to the clinical data using a 5-grade scale: 0 (normal), 1 (slight reduction of uptake), 2 (moderate reduction of uptake), 3 (severe reduction of uptake), and 4 (absence of radioactive uptake). The totals of the scores for all the segments during stress and at rest were designated as the summed stress score (SSS) and the summed rest score (SRS), respectively. SRS subtracted from SSS was defined as the summed difference score (SDS). Disagreements regarding image interpretation were resolved by consensus. If the difference score in each coronary territory was ≥1, myocardial ischemia was considered to be present.

CAG and FFR

All patients underwent CAG within 3 months of MPI. Multidirectional CAG was performed using Judkin's technique in all patients. The degree of coronary artery stenosis was visually rated according to the criteria of the American Heart Association [18]. The coronary angiographic data were evaluated by 2 cardiologists who were blinded to the clinical data. The measurements of 37 patients were obtained using Quantitative Coronary Angiography (QCA) software. Lesion length, proximal and distal reference diameters (acquired in the 5 mm non-affected segments next to the proximal and distal edges of the lesion), minimum lumen diameter (MLD) of the lesion, average of the proximal and distal reference diameters (RD), and percent diameter stenosis [DS: (RD − MLD)/RD] were obtained. QAngio XA software version 7.3 (Medis Medical Imaging Systems, Leiden, the Netherlands) was introduced for measurement from 2 images of different views. Furthermore, we evaluated semiquantitative calcification scores. In 39 cases, each patient's coronary arteries were divided into a total of 9 segments [left main diagonal coronary artery (LMD) as 1, left anterior descending coronary artery (LAD) into 3, left circumflex coronary artery (LCX) into 2, and right coronary artery (RCA) into 3] [19], and the extent of calcification for each segment was evaluated on a scale from 0 to 3 [20], and further summed as the calcification score of the patient. FFR measurement was dependent on the decision of the operators basically whether the target lesion was indicated for coronary intervention. A 0.014-in. guidewire with a mounted pressure sensor (Pressure Wire, St. Jude Medical, St. Paul, MN, USA or PrimeWire Prestige pressure guidewire, Volcano Corporation, San Diego, CA, USA) was placed across the lesion. To induce a maximal hyperemic vascular response, 8 mg and 12 mg of papaverine hydrochloride, a vasodilator of resistance vessels, were injected into the right and left coronary arteries, respectively. It has been reported that there is little difference in the effect of vasodilation between ATP and papaverine [21]. Under conditions of maximum hyperemia, simultaneous recording of aortic pressure and distal coronary pressure was performed. FFR was calculated as the ratio of hyperemic mean distal coronary pressure to mean aortic pressure [3,22]. The cut-off value for FFR for detecting myocardial ischemia was determined by receiver operating characteristic (ROC) curve analysis.

Statistical analysis

The results are expressed as mean ± SD, or number and frequency. The Student *t*-test was used to compare the means of the continuous variables. A *p*-value of <0.05 was considered to indicate a statistically significant difference. ROC curves were used to determine the cut-off value of FFR and the area under the curve (AUC). On the basis of the cut-off values of FFR and MPI, the patients were divided into 3 groups: concordant group, false-positive group, and false-negative group (Fig. 1). We compared the 3 groups by analysis of variance (ANOVA). SPSS (version 22.0; SPSS Inc., IBM Company, Chicago, IL, USA) and MedCalc 11.4 (MedCalc Software, Mariakerke, Belgium) were used for the statistical analysis.

Results

Patient characteristics

The clinical characteristics of the patients, including their medication at the time of the study, are summarized in Table 1. The