JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 70, NO. 17, 2017

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2017.09.007

Similarity and Difference of Resting Distal to Aortic Coronary Pressure and Instantaneous Wave-Free Ratio

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ABSTRACT

BACKGROUND Instantaneous wave-free ratio (iFR) has been used in clinical practice to identify functionally significant stenosis and to guide treatment strategy. However, there are limited clinical data regarding another resting pressure-derived index, resting distal to aortic coronary pressure (Pd/Pa), and similarities and differences between resting Pd/Pa and iFR.

OBJECTIVES The authors investigated the changes in resting Pd/Pa and iFR according to anatomic and hemodynamic stenosis severity and their prognostic implications.

METHODS From the 3V FFR-FRIENDS (Clinical Implication of 3-vessel Fractional Flow Reserve) and the IRIS-FFR (Study of the Natural History of FFR Guided Percutaneous Coronary Intervention) studies, 1,024 vessels ($n = 435$) with available pre-intervention resting Pd/Pa and iFR were used to explore the changes in resting physiological indices according to percent diameter stenosis. Among 115 patients who underwent ^{13}N-ammonia positron emission tomography, the changes in those indices according to basal and hyperemic stenosis resistance and absolute hyperemic myocardial blood flow were compared. The association between physiological indices and the risk of 2-year major adverse cardiac events (MACE) (a composite of cardiac death, myocardial infarction, and ischemia-driven revascularization) were analyzed among 375 deferred patients.

RESULTS There was a significant linear correlation between resting Pd/Pa and iFR ($R = 0.970$; $p < 0.001$, $iFR = 1.370 \times$ resting $Pd/Pa - 0.370$). Both resting Pd/Pa and iFR changed significantly according to percent diameter stenosis, basal and hyperemic stenosis resistance, and hyperemic absolute myocardial blood flow (all p values <0.001). Percent difference of iFR according to the increase in anatomic and hemodynamic severity was higher than that of resting Pd/Pa. Both resting Pd/Pa and iFR showed a significant association with the risk of 2-year MACE (resting Pd/Pa hazard ratio [per 0.10 increase]: 0.480; 95% confidence interval: 0.250 to 0.923; $p = 0.027$; iFR hazard ratio [per 0.1 increase]: 0.586; 95% confidence interval: 0.373 to 0.919; $p = 0.020$) in deferred patients. However, the difference between the upper- and lower-bound estimated MACE rates according to the approximate measurement variability of each index was significantly higher with resting Pd/Pa compared with iFR (resting Pd/Pa $3.85 \pm 4.00\%$ and iFR $3.27 \pm 3.39\%$; $p < 0.001$).

CONCLUSIONS Both resting Pd/Pa and iFR showed similar associations with anatomic and hemodynamic stenosis severity and the risk of MACE. However, iFR was more sensitive to the difference in stenosis severity and showed a lower maximum difference in estimated MACE risk influenced by the measurement variability compared with resting Pd/Pa. (Clinical Implication of 3-Vessel Fractional Flow Reserve [3V FFR-FRIENDS]; NCT01621438; and Study of the Natural History of FFR Guided Percutaneous Coronary Intervention [IRIS-FFR]; NCT01366404) (J Am Coll Cardiol 2017;70:2114–23) © 2017 by the American College of Cardiology Foundation.

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Identification of functionally significant coronary stenosis and ischemia-directed percutaneous coronary intervention (PCI) has been standard practice for patients with coronary artery disease. Fractional flow reserve (FFR) has been regarded as a reference invasive method to evaluate the functional significance of epicardial coronary artery stenosis (1,2). Recently, a physiological index that does not require hyperemia, instantaneous wave-free ratio (iFR), was introduced, and 2 randomized controlled trials showed noninferiority of iFR-guided strategy compared with FFR-guided strategy in terms of 1-year clinical outcomes (3,4). Although iFR is measured during rest, it is different from the whole-cycle resting distal to aortic coronary pressure (resting Pd/Pa) and relies on the identification of a wave-free period during diastole in which microvascular resistance is stable (5,6). Despite this methodological difference between resting Pd/Pa and iFR, previous studies reported an equivalent diagnostic performance of resting Pd/Pa and iFR using FFR (7-13) or the parameters from positron emission tomography (PET) as the reference standard (14). However, there was no study that comprehensively evaluated the similarity and difference between these 2 resting pressure-derived indices beyond the comparison of diagnostic performance.

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We sought to explore the similarity and difference between resting Pd/Pa and iFR in response to anatomic and hemodynamic stenosis severity and their association with clinical outcomes.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The study population was derived from the 3V FFR-FRIENDS study (Clinical Implication of 3-Vessel Fractional Flow Reserve; NCT01621438) (15) and IRIS-FFR registry (Study of the Natural History of FFR Guided Percutaneous Coronary Intervention; NCT01366404) (16). In both studies, patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-segment elevation myocardial infarction (MI) within 72 h, previous coronary artery bypass graft surgery, chronic renal disease, abnormal epicardial coronary flow (Thrombolysis In Myocardial Infarction flow grade <3) or planned coronary artery bypass graft surgery after diagnostic angiography were excluded. When PCI was indicated, coronary interventions were performed using current standard techniques. For lesions with significant per-vessel FFR (≤0.80), PCI was recommended as per the current guideline. However, the decision for PCI was at the discretion of the operators.

Among the total population, 1,024 vessels (435 patients) with available iFR and resting Pd/Pa were included in the current study. Among these patients, 115 patients who underwent ^{13}N-ammonia PET within 3 months of invasive physiological study for single lesion in the left anterior descending coronary artery (17) were analyzed as a PET subcohort. The study protocol was approved by the institutional review board or ethics committee at each participating center and all patients provided written informed consent.

ABBREVIATIONS AND ACRONYMS

%DS = percent diameter stenosis

BSR = basal stenosis resistance

CI = confidence interval

FFR = fractional flow reserve

HR = hazard ratio

HSR = hyperemic stenosis resistance

iFR = instantaneous wave-free ratio

IQR = interquartile range

MACE = major adverse cardiac events

MBF = myocardial blood flow

MI = myocardial infarction

PCI = percutaneous coronary intervention

Pd/Pa = distal to aortic coronary pressure

PET = positron emission tomography

^{13}N-AMMONIA PET PROTOCOL AND QUANTIFICATION OF ABSOLUTE MYOCARDIAL BLOOD FLOW. The ^{13}N-ammonia PET protocol and quantification of absolute myocardial blood flow (MBF) were presented previously (17). Briefly, all ^{13}N-ammonia PET images were acquired at baseline and in hyperemic states by continuous intravenous infusion of adenosine (140 μg/kg/min), started 3 min before the stress scan, employing low-dose computed tomography to correct for scatter and attenuation. A bolus of ^{13}N-ammonium (370 MBq) was injected via peripheral vein in both resting and hyperemic states, and list mode dynamic imaging was performed using a Siemens Biograph-40 PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany). A 2-compartment model was applied to quantify absolute MBF (ml/min/g). In PET images, the 6 basal segments were not quantified due to low counts in membranous interventricular septum and artifacts. Parametric stress MBF polar maps were used to delineate defect areas in target myocardial territories and to obtain MBF values of target segments. For image analysis and quantification of resting and stress absolute MBF in milliliters per minute per

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Manuscript received August 5, 2017; revised manuscript received August 26, 2017, accepted September 6, 2017.