JACC: CARDIOVASCULAR INTERVENTIONS VOL. ■, NO. ■, 2018

PUBLISHED BY ELSEVIER

Sex Differences in Adenosine-Free Coronary Pressure Indexes

A CONTRAST Substudy

Sonia V. Shah, MD,[a,b] Frederik M. Zimmermann, MD,[c] Nils P. Johnson, MD, MS,[d] Takeshi Nishi, MD, PhD,[a,b] Yuhei Kobayashi, MD,[a,b] Nils Witt, MD, PhD,[e] Colin Berry, MBChB, PhD,[f,g] Allen Jeremias, MD, MSc,[h,i] Bon-Kwon Koo, MD, PhD,[j] Giovanni Esposito, MD, PhD,[k] Gilles Rioufol, MD, PhD,[l] Seung-Jung Park, MD, PhD,[m] Keith G. Oldroyd, MBChB, MD,[f] Emanuele Barbato, MD,[k,n] Nico H.J. Pijls, MD, PhD,[c,o] Bernard De Bruyne, MD, PhD,[n] William F. Fearon, MD,[a,b] on behalf of the CONTRAST Study Investigators

ABSTRACT

OBJECTIVES The goal of this study was to investigate sex differences in adenosine-free coronary pressure indexes.

BACKGROUND Several adenosine-free coronary pressure wire indexes have been proposed to assess the functional significance of coronary artery lesions; however, there is a theoretical concern that sex differences may affect diagnostic performance because of differences in resting flow and distal myocardial mass.

METHODS In this CONTRAST (Can Contrast Injection Better Approximate FFR Compared to Pure Resting Physiology?) substudy, contrast fractional flow reserve (cFFR), obtained during contrast-induced submaximal hyperemia, the instantaneous wave-free ratio (iFR), and distal/proximal coronary pressure ratio (Pd/Pa) were compared with fractional flow reserve (FFR) in 547 men and 216 women. Using FFR ≤0.8 as a reference, the diagnostic performance of each index was compared.

RESULTS Men and women had similar diameter stenosis ($p = 0.78$), but women were less likely to have FFR ≤0.80 than men (42.5% vs. 51.5%, $p = 0.04$). Sensitivity was similar among cFFR, iFR, and Pd/Pa when comparing women and men, respectively (cFFR, 77.5% vs. 75.3%, $p = 0.69$; iFR, 84.9% vs. 79.4%, $p = 0.30$; Pd/Pa, 78.8% vs. 77.3%, $p = 0.78$). cFFR was more specific than iFR or Pd/Pa regardless of sex (cFFR, 94.3% vs. 95.8%, $p = 0.56$; iFR, 75.6% vs. 80.1%, $p = 0.38$; Pd/Pa, 80.6% vs. 78.7%, $p = 0.69$). By receiver-operating characteristic curve analysis, cFFR provided better diagnostic accuracy than resting indexes irrespective of sex ($p \leq 0.0001$).

CONCLUSIONS Despite the theoretical concern, the diagnostic sensitivity and specificity of cFFR, iFR, and Pd/Pa did not differ between the sexes. Irrespective of sex, cFFR provides the best diagnostic performance. (J Am Coll Cardiol Intv 2018;■:■-■) © 2018 by the American College of Cardiology Foundation.

From the [a]Stanford University School of Medicine, Stanford, California; [b]Stanford Cardiovascular Institute, Stanford, California; [c]Catharina Hospital, Eindhoven, the Netherlands; [d]McGovern Medical School at UTHealth and Memorial Hermann Hospital, Houston, Texas; [e]Karolinska Institutet, Södersjukhuset, Stockholm, Sweden; [f]West of Scotland Heart and Lung Center, Golden Jubilee National Hospital, Clydebank, United Kingdom; [g]British Heart Foundation Glasgow Cardiovascular Research Center, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom; [h]Division of Cardiovascular Medicine, Stony Brook University Medical Center, Stony Brook, New York; [i]Cardiovascular Research Foundation, New York, New York; [j]Seoul National University Hospital, Seoul, South Korea; [k]University of Naples Federico II, Naples, Italy; [l]Hospices Civils de Lyon and CARMEN, Lyon, France; [m]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea; [n]Cardiovascular Center Aalst, Aalst, Belgium; and [o]Eindhoven University of Technology, Eindhoven, the Netherlands. Dr. Fearon receives research support from ACIST Medical Systems, Abbott, Medtronic, and CathWorks and has a consulting relationship with HeartFlow and Boston Scientific. Dr. Jeremias is a consultant for Abbott Vascular and Philips and a member of the Speakers Bureau for Medtronic. Dr. Pijls has received institutional research grants from St. Jude Medical, Abbott, and Maquet and is a consultant for St. Jude Medical, Boston Scientific, and Opsens. Dr. Oldroyd has received institutional research support and consulting fees from Abbott Vascular and Boston Scientific. Dr. De Bruyne has received institutional research grants from Abbott, Boston Scientific, and Biotronik, and the Cardiovascular Research Center Aalst receives consultancy fees on his behalf from St. Jude Medical, Boston Scientific, and Opsens. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 12, 2018; revised manuscript received March 21, 2018, accepted March 21, 2018.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2018.03.030

ABBREVIATIONS AND ACRONYMS

cFFR = contrast fractional flow reserve

DS = diameter stenosis

FFR = fractional flow reserve

IC = intracoronary

ICC = intraclass correlation coefficient

iFR = instantaneous wave-free ratio

Pd/Pa = resting distal pressure/aortic pressure

ROC = receiver-operating characteristic

Physiological assessment of coronary stenosis by fractional flow reserve (FFR) has emerged as the gold standard to facilitate decisions regarding coronary revascularization (1-4). Studies of sex differences in FFR measurements have shown that in comparison with men, angiographic lesions of similar visual severity are less likely to be ischemia producing in women (5-7). In light of multiple prior studies that have found women undergoing percutaneous coronary intervention to have worse short- and long-term outcomes compared with men (8-10), an FFR-guided approach is particularly appealing in women to guide appropriate revascularization.

FFR measurement requires the induction of maximal hyperemia, which adds a small amount of time and cost to the procedure (11-13). Use of resting pressure indexes, which avoid the need for hyperemia, has been proposed, but studies have found these indexes to be less accurate compared with FFR (9,12,14-18). Recently, the CONTRAST (Can Contrast Injection Better Approximate FFR Compared to Pure Resting Physiology?) study investigated whether contrast medium (contrast FFR [cFFR]), which is ubiquitous in the catheterization laboratory and creates partial hyperemia, could provide an easy alternative and inexpensive tool for assessing FFR. The study found that cFFR was diagnostically superior to resting measurements, specifically resting distal pressure/aortic pressure (Pd/Pa) and the instantaneous wave-free ratio (iFR), in predicting FFR (19).

The reason for higher FFR values observed in women at maximum hyperemia is not entirely clear, but studies speculate this difference may be due to the smaller myocardial mass, vessel size, and territory associated with women (5,20). Other studies have cited microvascular dysfunction and impaired coronary autoregulation in women as a possible explanation for the greater anatomic-functional mismatch (5,21-26). There is a theoretical concern that microvascular dysfunction and differences in coronary physiology between men and women may also affect the diagnostic accuracy of adenosine-free indexes. Given this uncertainty, the primary goal of this study was to determine: 1) if the accuracy of adenosine-free indexes (cFFR, Pd/Pa, and iFR) varies by sex; and 2) if cFFR is diagnostically superior to resting pressure indexes regardless of sex.

METHODS

We explored the impact of sex in a post hoc analysis of the CONTRAST study (NCT02184117). The detailed study protocol and primary results have been published previously (19). In brief, the CONTRAST study is a multicenter, prospective, investigator-initiated observational study evaluating the diagnostic performance of cFFR, Pd/Pa, and iFR to predict FFR.

STUDY POPULATION. Subjects were recruited from 12 centers between June 2014 and April 2015. This study was approved by an institutional review committee from each participating site, and informed consent was obtained from all participants. Subjects underwent invasive physiological assessment of coronary artery lesions for standard clinical indications with comprehensive coronary physiological assessment, including both adenosine-free indexes and FFR. Subjects were excluded if they had previous coronary artery bypass surgery, an extremely tortuous or calcified coronary artery, known severe left ventricular hypertrophy, left ventricular ejection fraction of <30%, inability to receive adenosine, renal insufficiency such that additional contrast would pose unwarranted risk, or recent ST-segment elevation myocardial infarction. Culprit lesions for either ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction were excluded. Standard demographic, clinical, and catheterization parameters were collected for each subject.

STUDY DESIGN. The physiology protocol and core laboratory analysis used for the study have been previously described (19). Briefly, an initial period of at least 1 min provided a stable assessment of resting physiology without further contrast injection. This formed the basis of resting Pd/Pa and iFR determinations. Next, a manual or injector-based intracoronary (IC) bolus of contrast medium was given as per local practice for diagnostic angiography.

After pressure recovery, this was repeated. Following the return of baseline conditions, 100 to 200 mg of IC adenosine was administered as per local practice and repeated after pressure recovery. Next, intravenous adenosine was administered at a standard rate of 140 μg/kg/min for at least 2 min after pressure recovery through a central or antecubital vein. After stopping the intravenous infusion and waiting for the return of baseline conditions, another intravenous adenosine infusion at the same rate was performed.