

## LETTER TO THE EDITOR

# It All Depends on Your References: Electrophysiology Compared to Angiography

Michael Imhoff, M.D., Ph.D<sup>\*,†</sup> and Norbert Rainford, M.D.<sup>1</sup>

From the <sup>\*</sup>Department for Medical Informatics, Biometrics and Epidemiology, Ruhr-University, Bochum, Germany; and <sup>†</sup>qttec-group, Lübeck, Germany

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To the Editor,

In response to the publication of the article by Kawaji et al. in this journal, describing a study comparing Premier Heart's Multifunction Cardiogram (MCG) with coronary angiography (CAG) including quantitative coronary angiography (QCA), and fractional flow reserve (FFR) in the assessment of coronary artery disease (CAD),<sup>1</sup> we have significant concerns about the conduct, results and interpretation of the study.

The authors enrolled 100 stable patients over a time span of 6 months but only 89 were actually included. Given the wide inclusion criteria for a study at one of the leading cardiology centers in Japan it must be assumed that those 89 patients represented a fraction of the eligible patients. Moreover, nearly 50% of the patients were 75 years or older which even by Japanese population standards seems to be a distribution skewed toward elderly patients. Therefore, a relevant selection bias cannot be ruled out.

A second concern is that hemodynamically relevant collateral circulation was apparently not considered in the analysis of the CAG findings. As the goal of this study was to identify

hemodynamically relevant stenosis, collateral circulation should have been an important consideration. Anatomic-physiologic discordance is a known phenomenon with collateral circulation as a major cause.<sup>2</sup> This has been also shown in the first validation study of MCG.<sup>3</sup> Moreover, Premier Heart in every patient report also cautions that collateral circulation is a contributing cause of false negative results. This oversight calls into question the reliability of the reference method used by the authors for functionally relevant CAD.

Another aspect is the relatively high percentage of diabetes patients who are known to have the nonobstructive "lumpy bumpy" disease. Yet the authors chose not to perform FFR on the subset with 30% or less obstruction, assuming FFR was negative. Overall, FFR was performed in only less than 50% of all patients, although the authors considered FFR an important indicator of hemodynamic relevance of the observed angiographic lesions.

It should also be noted that the calculation of a mean severity score for the assessment of CAD does not comply with the instructions for use of MCG.

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Address for correspondence: Michael Imhoff, M.D. Ph.D, Buchenweg 18CD-23568, Lübeck, Germany. Fax: +49-451-707698-29; E-mail: mike@imhoff.de

<sup>1</sup>Formerly at Columbia Presbyterian Medical Center, New York; now in private practice.

Conflicts of interest: Dr. Imhoff is medical director of qttec-group, Lübeck, Germany, a service provider (regulatory, quality management) for the medical device industry, and senior advisor at Boston MedTech Advisors, Inc., Dedham, MA, a consulting firm for the medical device industry.

Thus far four independent prospective studies, published in peer-reviewed journals, have consistently and reproducibly shown high sensitivity and specificity of MCG in the prediction of hemodynamically relevant coronary stenosis detected in coronary angiography.<sup>3,6</sup> In all these clinical trials, which showed a good to excellent diagnostic accuracy of MCG, a cutoff point of 70% of large caliber epicardial coronary arteries and a 50% left main obstructive disease have always been used to compare with MCG assessed ischemia at MCG Severity Scores greater or equal to 4.0 in the presence of local or global ischemia.

Although the authors discussed the discrepancy between their findings in 89 patients and those of the four MCG validation studies involving nearly 1100 patients, it is very difficult to conclude that the investigative methods of four prior independent studies involving larger and more diverse patient selection were in error.

Another very recent study from Japan by Amano et al. comparing MCG also with CAG and FFR reached conclusions that were very comparable to the MCG validation studies.<sup>7</sup> Also, a study by Strobeck et al. comparing MCG with SPECT and CAG concluded that MCG has high predictive value for the presence of hemodynamically relevant CAD.<sup>8</sup>

Finally, in the most recent analysis published by Kawaji et al. using the same dataset as in their article mentioned above but with different reference MCG severity scores, the authors came to the contrasting conclusion that "MCG with severity score and supplemental reports had high sensitivity to detect angiographic coronary atherosclerosis, and appeared to be useful for noninvasive screening of coronary atherosclerosis."<sup>9</sup>

Therefore, that study by Kawaji et al. published in this journal raises more concerns about the validity of the reference method employed than it tells about the clinical utility of MCG.

## REFERENCES

1. Kawaji T, Shiomi H, Morimoto T, et al. Noninvasive detection of functional myocardial ischemia: Multifunction cardiogram evaluation in diagnosis of functional coronary ischemia study (MED-FIT). *Ann Noninvasive Electrocardiol* 2015;20(5):446-453.
2. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol* 2013;62:1639-1653.
3. Weiss MB, Narasimhadevara SM, Feng GQ, et al. Computer-enhanced frequency-domain and 12-lead electrocardiography accurately detect abnormalities consistent with obstructive and nonobstructive coronary artery disease. *Heart Dis* 2002;4:2-12.
4. Grube E, Bootsvelde A, Buellesfeld L, et al. Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis after coronary revascularization. *Int J Med Sci* 2008;5:50-61.
5. Grube E, Bootsvelde A, Yucel S, Shen JT, Imhoff M. Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis. *Int J Med Sci* 2007;4:249-263.
6. Hosokawa J, Shen JT, Imhoff M. Computerized 2-lead resting ECG analysis for the detection of relevant coronary artery stenosis in comparison with angiographic findings. *Congest Heart Fail* 2008;14:251-260.
7. Amano T, Shinoda N, Kunimura A, et al. Noninvasive assessment of functionally significant coronary stenoses through mathematical analysis of spectral ECG components. *Open Heart* 2014;1:e000144.
8. Strobeck JE, Mangieri A, Rainford N. A paired-comparison of the Multifunction Cardiogram (MCG) and sestamibi SPECT myocardial perfusion imaging (MPI) to quantitative coronary angiography for the detection of relevant coronary artery obstruction ( $\geq 70\%$ )—a single-center study of 116 consecutive patients referred for coronary angiography. *Int J Med Sci* 2011;8:717-724.
9. Kawaji T, Shiomi H, Ryusuke N, et al. Validation of multifunction electrocardiogram (MCG) in screening of ischemic heart disease. *J. Clin Therapeut Med* 2015;31:57-61.