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Reply: Caffeine and fractional flow reserve overestimation: a word of caution

Hidenari Matsumoto*, MD, PhD

Division of Cardiology, Showa University School of Medicine, Tokyo, Japan

The letter by Siig et al[1] raises a question about caffeine's antagonism to adenosine-induced coronary hyperaemia, in connection with our recent publication[2], by quoting a paper by Kasumi et al[3]. They showed no relationship between adenosine triphosphate-induced hyperaemia and caffeine intake before fractional flow reserve (FFR) measurements. The paper, however, has critical limitations. First, they evaluated the time from the last caffeine intake alone and did not measure serum caffeine levels, which precluded any conclusion on the effect of caffeine on adenosine-induced FFR (FFR_{ADN}). Other than the time from the last caffeine intake, several factors influence serum caffeine levels, including habitual caffeine consumption, caffeine concentration or dose in food or beverages recently ingested, and the wide variation in the half-life of caffeine. Secondly, nicorandil was used as a comparator of adenosine triphosphate. Historically, the hyperaemic efficacy of adenosine has been validated against papaverine[4,5], which is the most reliable agent for maximal hyperaemia induction[6,7]. Although nicorandil-induced FFR values were not statistically different from FFR_{ADN} values in validation studies for nicorandil FFR, the Bland-Altman limits of agreement were quite large[8,9]. Additionally, the reports did not provide any information on serum caffeine levels and caffeine abstinence. Moreover, we recently demonstrated that nicorandil was inferior to papaverine in terms of hyperaemic efficacy[7].

The authors hypothesise that caffeine, which binds to adenosine receptors, acts as a hyperaemic agent, which leads to FFR_{ADN} underestimations. This is an incoherent argument. It has been validated that caffeine antagonises the pharmacologic actions of adenosine by competitively blocking adenosine receptor activity[10]. Our data demonstrated that serum caffeine level was the strongest factor associated with FFR_{ADN} overestimation in the multivariable analysis[2]. Since FFR is the ratio of the mean distal coronary artery pressure (Pd) to the mean aortic pressure (Pa) during maximal hyperaemia – the lowest achievable Pd/Pa value – the term "FFR underestimation" does not make any sense.

Finally, the letter notes sex differences in caffeine antagonism to adenosine-induced hyperaemia. In a recently published Rubidium-82 positron emission tomography study conducted on healthy young volunteers, caffeine influenced adenosine-induced myocardial blood flow and myocardial flow reserve at lower serum caffeine levels in men than in women[11]. This is an interesting standpoint. Microvascular function and adenosine receptor expression may differ between the sexes. Nevertheless, the result from healthy volunteers cannot be applied to adenosine-induced FFR measurements in older patients with coronary atherosclerosis or impaired microvascular function. Furthermore, the use of Rubidium-82 with a well-known roll-off phenomenon[12] is also a major limitation of the study. In our study, the result was consistent, regardless of sex.

The effect of caffeine on FFR_{ADN} is clinically relevant. Further investigation is warranted with a larger cohort of patients composed of different ethnic groups.

Conflict of interest statement

The author has no conflicts of interest to declare.

*Corresponding author: Division of Cardiology, Showa University School of Medicine, 1-5-8 Hatanodai Shinagawa-ku, Tokyo 142-8555, Japan. Email: matsumoto.hidenari@med.showa-u.ac.jp

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