Hold off on that shot of Java: more evidence that caffeine intake leads to false negative adenosine stress myocardial perfusion

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The presence of coronary atherosclerosis can lead to impaired myocardial perfusion. There is near universal consensus that abnormal myocardial perfusion should guide the decision whether or not invasive treatment is warranted [1]. In clinical practice a variety of diagnostic tests are commonly used to establish impaired myocardial perfusion. Today the most widely used tests are single photon-emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance myocardial perfusion imaging (MR-MPI) [2]. An important drawback of these techniques is the need for injection of an exogenous tracer or contrast agent. Apart from the costs associated with these approaches there is also a small but non-negligible risk for acute and chronic side-effects.

A promising alternative technique to assess myocardial perfusion is non contrast-enhanced or ‘native’ myocardial T1 mapping. Native T1 mapping is a novel MRI technique that can potentially detect myocardial ischemia as well as infarcted myocardium by direct assessment of myocardial water content. T1 is a magnetic property of tissue that is prolonged by increased water content. In a recent study, Liu et al. found that normal, infarcted, ischemic myocardium can be differentiated by native T1 mapping at rest and during adenosine stress because these tissues classes exhibit distinctive T1 profiles. Compared to resting conditions, myocardial T1 values during adenosine stress increased approximately 6% both at 1.5 and 3.0T field strengths in

normal myocardium, whereas in ischemic myocardium the change in T1 was negligible [3]. Although these authors studied a small number of patients and did not report test–retest reproducibility data, the study is promising as it potentially allows for safer, more efficient and cheaper MRI examinations.

An important confounder of the response to adenosine-induced myocardial vasodilatation is caffeine. Caffeine (1,3,7-trimethylxanthine) is one of the most widely consumed stimulants worldwide with over 80% of the US population reporting daily intake [4]. Individuals primarily consume caffeine for a variety of behavioral effects such as changes in mood, energy and alertness [5]. Caffeine is present in coffee, tea, a variety of different soft drinks, energy drinks as well as cacao products and many fruits and vegetables. In the US approximately 75% of caffeine intake is attributable to coffee consumption with estimated mean intake of approximately 180 mg/day [4]. A number of studies have investigated the effect of caffeine on adenosine stress myocardial perfusion imaging, but there is no consensus on whether inadvertent intake should lead to postponement of a planned examination [6, 7].

Given that native T1-mapping is sensitive to the increase in myocardial water content induced by adenosine administration, one could imagine that this technique can potentially be used to assess adequacy of vasodilator induced myocardial hyperaemia. In this issue of *IJCVI* Kuijpers et al. [8] propose that the native T1 response can be used to assess the adequacy of adenosine-induced stress myocardial hyperperfusion. This would provide a quantitative measure of whether a patient is adequately stressed and would be a significant improvement over currently used methods. In their study, rest and stress T1 mapping was performed in 10 patients who inadvertently drank coffee between 24 and 8 h prior to the MRI examination, 15 patients who drank

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coffee within 4 h of the MRI examination and a group of 80 control subjects who reported no caffeine consumption in the 24 h prior to the MRI examination. Of these 80 patients, 50 patients had normal MRI results, 18 had myocardial ischemia and 12 patients had prior myocardial infarction. Changes in native T1 values were compared as a function of self-reported coffee consumption as well as the presence or absence coronary artery disease. T1 relaxation times were determined in the interventricular septum in every subject as well as in areas with perfusion defects and infarcts. The presence of perfusion defects and infarcts was assessed using contrast-enhanced adenosine stress MR-MPI and delayed enhancement imaging. Compared to controls without caffeine intake and normal perfusion, patients who reported caffeine intake in the 24 h prior to the adenosine stress MR examination were found to have a markedly attenuated T1-response. Whereas native T1 values *increased* $4.3 \pm 2.8\%$ in subjects who did not consume caffeine, T1 values *decreased* by $7.8 \pm 5.0\%$ in the group of subjects who consumed caffeine <4 h before the examination, and increased by just $1.8 \pm 4.0\%$ in subjects reporting caffeine intake between 8 and 24 h prior to the examination. There was very little change in T1 value in areas with perfusion defects ($0.2 \pm 0.7\%$), and areas with infarcts ($0.3 \pm 0.4\%$). Interestingly, in patients who had evidence of ischemia or infarction, remote, visually normal myocardium also exhibited an attenuated T1 response compared to patients without ischemia or infarction. From these data the authors conclude that the change in myocardial native T1 value between rest and stress can serve as a measure of stress adequacy and should be reported in the radiology report.

How can these findings be explained? The normal response to adenosine administration is vasodilatation of precapillary coronary arterioles, resulting in an approximately 2.5- to 3.5-fold increase myocardial blood flow [9] in segments subtended by normal coronary arteries. Due to the resultant increase in myocardial blood volume the increase in perfusion leads to measurable changes in T1 values. Mahmood et al. [10] calculated that the expected increase in T1 relaxation time is indeed expected to be in the range of 5–6%, assuming that a threefold increase in flow leads to approximately a doubling of the intramyocardial blood volume, i.e. from an estimated 10% at rest to 20% during maximal hyperaemia. When cardiac adenosine receptors are blocked by caffeine, the intended precapillary vasodilation is severely attenuated, which may even lead to a decrease in myocardial blood flow and myocardial blood volume [11], and a reduction in myocardial T1 values.

In humans, caffeine is metabolized in the liver by the cytochrome P450 (CYP) enzyme CYP1A2 and healthy adults the half-life of caffeine is approximately 4–5 h [4]. However, there is substantial variation between males and females and different age groups; other important sources

of variation between individuals are frequency of caffeine intake, concurrent cigarette smoking and genetic variations in the adenosine receptors and downstream signaling cascade proteins [4]. As demonstrated by Kuijpers et al., native T1-mapping seems capable of detecting the blunting effects of caffeine consumption on adenosine-induced myocardial hyperaemia. Furthermore, the authors postulate that adenosine-induced change in native T1 values may be a more direct reflection of tissue oxygenation and myocardial ischemia when compared to fractional flow reserve. Indeed, it is well known that a pressure drop across a coronary stenosis does not necessarily result in decreased myocardial perfusion [12], and a more direct measure of downstream tissue perfusion without the need for injection of contrast agents would indeed be hugely valuable.

What do these findings mean for clinical practice? First, this study provides convincing evidence that caffeine consumption indeed influences myocardial perfusion when adenosine is used to induce myocardial hyperperfusion. In light of these findings it seems prudent to emphasize to patients to refrain from caffeine intake in the 24 h preceding the MRI examination. There are also some caveats that need further attention. Unfortunately, the authors did not repeat stress MR-MPI in all patients who consumed caffeine before the examination. Therefore, we do not know the proportion of patients with false negative MR-MPI results. In addition, blood caffeine levels were not determined and there is no information on test–retest variability in stress and at rest after caffeine consumption. These data are needed before native T1 mapping can be used clinically to assess stress adequacy. It also remains to be investigated whether caffeine blunts native myocardial T1 reactivity in the presence of other stressors such as the selective adenosine A_{2A} receptor blocker regadenoson (Lexiscan, Astellas Pharma, Northbrook, IL). A randomized, double-blind, placebo-controlled study of regadenoson-incubed myocardial hyperaemia with ^{15}O -labeled water PET by Gaemperli et al. [13] found no significant changes after ingestion of 200 mg caffeine prior to the examination.

In current clinical practice, the ‘splenic switch-off’ sign is often used as a measure of stress adequacy. The sign—a decrease in splenic contrast-enhancement during concurrent adenosine and gadolinium contrast agent infusion—occurs because adenosine mediates its effects on splenic perfusion via A_1 and/or A_{2B} adenosine receptors to maintain circulatory volume in conditions of shock, whereas coronary vasodilatation is mediated via the adenosine A_{2A} receptor [14]. Although this a very simple and useful way to identify patients at higher risk of a false-negative MR-MPI study, this sign can only be used post hoc, i.e. after contrast has been injected. The attractiveness of the approach by Kuijpers et al. is that it allows adequacy of stress induced hyperperfusion prior to contrast injection, and it provides further

evidence that native T1 mapping could potentially replace contrast-enhanced MR-MPI.

In conclusion, the study by Kuijpers et al. provides important new insights into the effects of caffeine on myocardial perfusion. In light of the reported results it seems wise to hold off on that shot of java before adenosine stress myocardial perfusion imaging.

Compliance with ethical standards

Conflict of interest None.

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