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● *Clinical Note*

# ASSESSMENT OF SYSTEMIC ADENOSINE EFFECT USING COLOR DOPPLER ULTRASOUND OF THE SPLENIC ARTERY—FEASIBILITY AND POTENTIAL CLINICAL UTILITY FOR CORONARY INTERVENTIONS

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**Abstract—Adenosine induces coronary vasodilation and simultaneously reduces splanchnic perfusion. This effect can be absent in adenosine non-responders. Imaging of splanchnic arteries under adenosine assessing this effect has not been performed in humans previously. In 26 patients, splenic artery color Doppler was performed during an infusion of adenosine. Peak velocity in the splenic artery was measured before the infusion and at 2 min. Results were compared qualitatively with perfusion imaging in magnetic resonance. A total of 24 patients showed a drop of splenic artery peak velocity from 62.3 ± 18.1 to 40.4 ± 15.7 cm/s ($p < 0.001$), which corresponded to perfusion restriction in magnetic resonance. Two patients with constant splenic artery velocity did not show perfusion restriction. We showed feasibility of assessing changes in splenic artery velocity under adenosine for the first time in humans. Further studies are needed to investigate whether this novel application is a robust tool to rule out inadequate adenosine effect during measurement of fractional flow reserve in coronary catheterization. (E-mail: o.klein-wiele@kk-essen.de)** **© 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

***Key Words:*** **Adenosine, Stress perfusion, Splenic artery, Splanchnic perfusion, Splenic switch-off sign, Cardiovascular magnetic resonance.**

## INTRODUCTION

Adenosine stress testing to assess myocardial perfusion in patients with known or suspected coronary artery disease (CAD) is well established in cardiologic patients. Three commonly applied diagnostic tools that use the vasodilatory effect of adenosine in the coronary circulation are available: adenosine stress cardiovascular imaging (cardiac magnetic resonance [CMR]) (American College of Cardiology Foundation Task Force on Expert Consensus D et al. 2010), measurement of the fractional flow reserve (FFR) during coronary interventions (Authors/Task Force M et al. 2014) and stress echocardiography (Djordjevic-Dikic et al. 1996).

The vasodilatory effect of adenosine and induction of hyperemia is mediated *via* $A_{2\,A}$-receptors in the coronary arteries (Headrick et al. 2011). Myocardial ischemia can be detected because of steal effects in stenosed coronary arteries (Gargiulo et al. 2013; Pontone et al. 2015). However, vasodilation under adenosine can be absent or insufficient for stress perfusion assessment because the drug may be degraded as a result of its short half-life before the coronary effect can be exhibited (Kidambi et al. 2016); various clinical conditions (*e.g.,* caffeine intake, usage of dipyridamole or theopylline, maximal vasodilation from concomitant illness such as cirrhosis) can also attenuate the circulatory adenosine effect (Layland et al. 2014). Therefore, adenosine stress may not be reliable to rule out stenoses. The typical side effects of adenosine are usually taken as an indicator for adequate adenosine effect. However, a drop in blood pressure, tachycardia or chest discomfort may not always be present (Manisty et al. 2015). In pacemaker-dependent patients, acceleration of heart rate (HR) is absent under adenosine, assessment of adenosine effect may be impaired.

In CMR, a helpful method has been established to assess adequacy of the adenosine effect (Manisty et al.

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2015): The "splenic switch-off" sign takes into account that adenosine simultaneous to coronary vasodilation reduces splanchnic artery perfusion *via* A1-receptors (Morato et al. 2008). Hence, delayed enhancement of the spleen compared with the myocardium can be observed under adenosine stress. In the absence of splenic switch-off, coronary vasodilation is estimated to be insufficient for ischemia detection in CAD (Manisty et al. 2015). Until now, only CMR data have existed on this phenomenon.

Our study aimed to investigate splenic artery velocity during adenosine administration with color Doppler. We intended to evaluate a bedside test to assess the adenosine effect in other applications of adenosine stress testing, as well (*e.g.,* in FFR measurement in coronary interventions). During FFR measurement, adenosine is used to induce maximum coronary dilation; the drop in coronary pressure across a stenosis is measured with a wire-mounted sensor. Insufficient vasodilation because of inadequate adenosine effect may be relevant also in this setting and may be misleading and underestimate stenosis.

## MATERIALS AND METHODS

The study complies with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave informed consent before inclusion. We prospectively analyzed a cohort of patients (n = 26; mean age 72.1 ± 7.8 y, 15 women) that underwent adenosine stress CMR in the presence of a magnetic resonance conditional pacemaker. For detailed baseline characteristics, see Table 1. CMR was performed with a 1.5-T wide bore system (ESPREE; Siemens Healthcare, Erlangen, Germany), using a 4-channel body array and an 8-channel spine coil. The maximum gradient field was 33 mT/m (Z-Engine) with a slew rate of 100 T/m/s. Maximum specific absorption rates were limited to 2.0 W/kg. In our routine protocol, we have established a test infusion of adenosine before CMR to assess adenosine's effect on HR. HR response under adenosine is considered for the selection of pacing modes: asynchronous stimulation in the case of bradycardia induced by adenosine, and deactivation of the pacemaker in the absence of bradycardia (Klein-Wiele et al. 2015).

Table 1. Baseline characteristics

| | | |
|---|---|---|
| Total patients | 26 | |
| Mean Age (y) | 72.1 ± 7.8 | |
| Body mass index | 29.1 ± 3.3 | |
| | N | % |
| Female | 15 | 15 |
| Pacemaker indication | | |
| Higher degree AV Block | 10 | 38.5 |
| Sinus node dysfunction | 15 | 57.8 |
| Bradyarrhythmia in AF | 1 | 2.8 |
| Coronary artery disease | 13 | 50.0 |
| Previous MI | 8 | 30.1 |
| Paroxysmal atrial fibrillation | 3 | 11.5 |
| Hypertension | 13 | 50.0 |
| Diabetes mellitus | 6 | 23.1 |
| Hypercholesterolemia | 16 | 61.5 |
| Smoker (current) | 5 | 19.2 |
| Pacemaker | | |
| Ensura MRI Sure Scan | 25 | 96.2 |
| Advisa DR MRI Sure Scan | 1 | 2.8 |
| Pacemaker-dependent (HR <30 beats/min) | 8 | 30.8 |

AV = atrioventricular, AF = atrial fibrillation, HR = heart rate, MI = myocardial infarction, MRI = magnetic resonance imaging.

During the test infusion, we visualized splenic perfusion using color Doppler. Color duplex sonography was performed with a 2–4-mHz curved linear array transducer (Vivid S6, General Electric, Fairfield, CT, USA). Patients were scanned in the supine position. An ultrasound probe covered with transmitting gel was placed on the skin at the left flank in the cranio-caudal orientation with no pressure to avoid mechanical compression on splenic vessels. Color-flow imaging was used to locate the splenic artery at the hilum. Color and spectral Doppler settings, including pulse repetition frequency and gain, were adjusted depending on blood flow velocity in the splenic artery. A 3–5 mm-spectral Doppler gate was placed at the center of the arterial lumen with a frequency of 2.5 MHz for acquiring the Doppler spectrum and a sweep of 50 mm/s for recording the spectrum.

Peak velocity in the splenic artery at baseline and at 2 min under an infusion of adenosine (140 ug/kg weight/min) was measured to detect possible velocity changes as an adenosine effect. Breath-hold time had to be limited because of respiratory symptoms induced by adenosine; therefore, measurement was performed only at 2 min, according to the time of measurement in CMR. Measurements were compared with splenic enhancement in CMR under adenosine, which was assessed qualitatively: Delayed splenic enhancement compared with myocardial enhancement was regarded as a sign for splenic perfusion restriction under adenosine, as previously described (Manisty et al. 2015). First-pass perfusion imaging was carried out with intravenous bolus administration of gadolinium (140 ug/kg weight/min) in a fast low-angle shot sequence at 2 min after starting the adenosine infusion, which was continued during the perfusion scan.

## RESULTS

A total of 24 patients showed a drop in splenic artery peak velocity from 62.3 ± 18.1 to 40.4 ± 15.7 cm/s ($p < 0.001$), corresponding to delayed splenic enhancement compared with myocardial enhancement in CMR. In two patients, splenic artery velocity did not show relevant changes under adenosine (baseline: 35.8 and 48.5; adenosine: 35.3 and 49.5, respectively); splenic switch-off was absent in CMR accordingly. Figure 1 presents an