Failed splenic switch-off – a simple clinical sign to improve the diagnostic performance of adenosine perfusion CMR

First author's surname: Manisty

Short title: Splenic perfusion with pharmacological stress

Charlotte Manisty [1,2], David P. Ripley[3], Anna S. Herrey[2], Gabriella Captur[2], Timothy C Wong C[5], Charles Peebles[4], Eric B Schelbert[5], John Greenwood[3], James C Moon[2]

1 International Centre for Circulatory Health, Imperial College London, UK

2 The Heart Hospital Imaging Centre and University College London, London UK

3 Multidisciplinary Cardiovascular Research Centre and Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, UK

4 Wessex Cardiothoracic Unit, Southampton University Hospitals NHS Trust, UK

5 Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, US

Correspondence: Dr James Moon
Tel:+44-2034563081
Fax:+44-2034563086
Email: j.moon@ucl.ac.uk

Abstract

Background: The sensitivity of adenosine perfusion CMR for ischemia is reduced by false negative scans, which may result from inadequate pharmacological stress. We observed that splenic perfusion is markedly attenuated by adenosine stress compared both to rest and to myocardial perfusion, so we investigated the pharmacology and clinical utility of 'splenic switch-off'.

Methods: We assessed splenic perfusion in CMR perfusion scans from 4 cohorts in 4 separate units using 3 different pharmacological stressors: 1) 50 adenosine scans (London, UK) to determine whether splenic perfusion is consistently visible and switched-off with adenosine; 2) and 3): comparison cohorts using alternative pharmacological stressors (25 dobutamine scans with perfusion; Southampton, UK and 25 regadenoson scans; Pittsburgh, US) to assess the pharmacology of splenic switch-off; and 4) 100 adenosine scans (35 false and 65 true negative) from the CE-MARC trial (Leeds,UK); to assess clinical utility in detecting inadequate stress.

Results: The spleen is visible in 98.5% of perfusion scans. Grading of splenic perfusion is reliable (concordance between 2 blinded observers, κ=0.84). Splenic switch-off occurred in 92% of adenosine studies but in none of either the dobutamine or regadenoson studies.

Semi-quantitatively, with adenosine, splenic perfusion is lower than at rest (8.1±9 versus 33±19 arbitrary units, $p<0.0001$); in contrast to with regadenoson (124±57 versus 145±59 au, $p=0.003$). With adenosine stress splenic perfusion is lower than myocardial perfusion, whereas it is higher with both regadenason and dobutamine.

Within the CE-MARC cohort, patients with false negative CMR scans had a 36% rate of failed splenic switch-off. By contrast, the true negative group had a 9% rate ($p=0.0027$ for difference).

Conclusion: Splenic switch-off with adenosine is a new, reliable observation, and specific to adenosine. Rescanning individuals with failure of splenic switch-off would reduce false negative scans by a third, but it may be that up to 1 in 11 of all adenosine perfusion patients are understressed. Further work is needed on this important sign.

Key words: Perfusion CMR, adenosine, sensitivity, splenic perfusion, negative predictive value, false negative

Introduction

The diagnostic performance of any functional test for the detection of myocardial ischemia is dependent on subjects being adequately stressed. Perfusion cardiovascular magnetic resonance (CMR) imaging is a safe, accurate and reproducible technique, with adenosine being the most common pharmacological agent used to induce stress by vasodilating the coronary vasculature and inducing hyperemia in myocardium where no stenosis is present. The sensitivity and negative predictive values of adenosine perfusion CMR, although comparable to SPECT, have however not improved significantly over 10 years since the introduction of the technique[1,2,3] with false negative rates of between 5 and 10%[4,5,1]. It is thought that up to 50% of these false negative scans result from patients receiving insufficient pharmacological stress to induce perfusion deficits; either because of drug interactions such as caffeine, or due to administration errors. Caffeine in particular may have a long half life, either in slow metabolizers, or with certain drugs (for example SSRI antidepressants; fluvoxamine for example may prolong its half life from 4.9 to56 hours[6]). Unlike dobutamine stress, where a pre-specified physiological response is targeted, adenosine stress follows a fixed protocol of 140mcg/kg/min for 3 minutes, although many centres augment to 170mcg/Kg/min for a further minute if there is no heart rate or symptom response.[78] This approach is not guaranteed to induce myocardial vasodilatation and maximal hyperaemia and, in the case of symptoms, is a rather subjective sign[93].

We observed during the reporting of routine clinical adenosine stress perfusion CMR imaging that there can be almost complete attenuation of contrast enhancement of the spleen during adenosine infusion compared to on resting images, a somewhat obscure observation but one which we find had been previously described in animal models.[10,11,12] Adenosine had one other observable abdominal visceral effect: intestinal peristalsis was reduced during perfusion. This is another recognised extra-cardiac effect of adenosine on the intestinal

smooth muscle cells[13], but it has not previously been reported to have been clearly observable on MRI images.

We hypothesised that a straightforward visual observation of splenic perfusion during adenosine infusion may therefore provide a window for assessing the adequacy of adenosine stress, with failure of 'splenic switch-off' alerting the operator and/or reporting physician to a potentially understressed patient who may require re-scanning.

Accordingly, we formed a multicentre collaboration to assess the pharmacology of splenic switch-off and determine its clinical potential as a tool for the detection of patients understressed by adenosine, with the goal of improving test sensitivity. We firstly observe whether splenic switch-off is a consistent CMR finding with adenosine. We then investigate whether this is the result of generic stress, or is a drug-specific effect of adenosine by observing splenic perfusion with regadenoson (a selective A_{2A} receptor agonist, marketed as Lexiscan in US, and Rapiscan in Europe) and dobutamine perfusion CMR scans. Coronary vasodilatation is mediated via the adenosine A_{2A} receptor, whereas it is the A_1, A_{2B}, and A_3 receptors that are responsible for the undesirable side effects associated with adenosine, Regadenoson is used for both perfusion CMR and SPECT imaging[9,14,15] because of its relative selectivity for coronary $A_{(2A)}$ receptors, with minimal extracardiac effects. If splenic switch-off with adenosine is not present with regadenoson or dobutamine, it indicates that this is a drug-specific effect, and helps to decipher the pharmacology of the sign.

Finally using a cohort of the CE-MARC dataset with both angiographic and perfusion CMR results, we assess the clinical utility of splenic switch-off to identify CMR scans subsequently shown to be false negatives.

Methods

Study data.

A retrospective observational study of splenic perfusion in 200 stress CMR scans performed using 3 different stressor agents, acquired in 4 separate institutions as follows:

- A verification cohort of 50 adenosine perfusion scans (The Heart Hospital, London, UK); to determine how often the spleen can be seen in routine perfusion CMR scans, whether splenic perfusion switch-off is a consistent finding; and whether it can be reproducibly graded.
- Two comparison cohorts using alternative pharmacological stressors to assess splenic switch-off is the result of generic stress or a drug-specific effect of adenosine. These were 25 randomly-selected dobutamine stress CMR scans acquired at Southampton General Hospital, UK and 25 randomly-selected regadenoson stress CMR scans acquired at University of Pittsburgh Medical Centre, USA.
- A clinical utility cohort from the CE-MARC trial[4], analysed to assess whether failure of splenic switch-off was clinically useful to detect inadequate stress. This dataset comprised 100 adenosine stress perfusion scans from the main CE-MARC trial (Leeds, UK), including firstly the entire cohort (n=35) of known false negative scans (normal CMR perfusion; >70% coronary stenosis by QCA X-ray coronary angiography), and secondly 65 randomly-selected true negative studies. For the false negatives, CE-MARC analysis of symptoms and heart rate response suggested that over half had presumed inadequate pharmacological stress. A difference in the rate of failed splenic switch-off in false compared to true negatives would indicate the clinical utility of the observation to detect under-stress.

Adenosine stress perfusion imaging – observational cohort

Splenic perfusion was assessed retrospectively in 50 adenosine perfusion CMR scans acquired for routine clinical purposes at The Heart Hospital Imaging Centre using standard protocols. Scans were performed using a 1.5 T (Siemens Avanto) clinical CMR scanner, with adenosine administered at a dose of 140mcg/kg/min for 4 minutes and extravascular contrast medium Dotarem (gadoterate meglumine) administered intravenously at 0.05 mmol/kg bodyweight. First pass perfusion imaging was performed every cardiac cycle using a T1-weighted saturation recovery gradient echo sequence with FLASH readout at stress and after 10 minutes of recovery, at rest.

Dobutamine stress CMR data

The dobutamine stress CMR scans were acquired in Southampton General Hospital for clinical indications and were performed according to standard protocols for regional wall motion abnormalities. However after the last cine acquisition, at peak stress, perfusion CMR was performed for its added value. Scans were acquired using a 1.5 T (Siemens Avanto) clinical CMR scanner, with dobutamine infused in 10 mcg/kg/min increments up to a maximum of 40 mcg/kg/min until target heart rate was achieved or a recognised stop indication reached. The perfusion CMR protocol was the same as at described for The Heart Hospital except that double dose (0.15 mmol/kg dimeglumine gadobenate) was administered, the 3 slice acquisition typically occurred over two heartbeats due to the high heart rates, and subsequent rest perfusion was omitted.

Regadenoson stress CMR data

Splenic perfusion was assessed in 25 regadenoson perfusion CMR scans acquired for routine clinical purposes at the UPMC CMR Center, US. Scans were performed using a 1.5 T (Siemens Espree) and regadenoson (0.4 mg bolus) followed by aminophylline (100 mg IV) reversal. First pass perfusion employed a steady state free precession (SSFP) readout after a

T1 weighted saturation recovery preparation with a 0.05 mmol/kg gadoteridol contrast agent. Rest perfusion images were acquired after a 10 minute delay.

Adenosine stress perfusion data (CE-MARC data)

The methods used in CE-MARC have been published previously[4,16]. In summary consecutive patients with suspected angina pectoris were screened and enrolled if they had at least one major cardiovascular risk factor and a cardiologist judged them to have likely stable angina needing investigation (the prevalence of significant coronary disease in this population was estimated to be 40–60%). Patients underwent invasive X-ray coronary angiography, adenosine perfusion CMR and (in a majority) SPECT imaging. All CMR images were acquired on a 1·5 T Philips Intera CV scanner (Philips Healthcare, Best, Netherlands), and the CMR result ('positive' or 'negative') was reported at the time of the CE-MARC trial based on ventricular function, perfusion and scar on late gadolinium enhancement imaging. First pass perfusion was compared at rest and following 4 minutes of intravenous infusion of adenosine at a dose of 140 mcg/kg per min, using 0·05 mmol/kg dimeglumine gadopentetate (Multihance; Bracco SpA; Milan, Italy) as contrast agent for each. For CE-MARC a gold standard of X-ray coronary angiography was used, against which the CMR results were compared (after the perfusion scans were performed and interpretation locked), and in this current study we use 'false' and 'true' negatives as originally reported, with no re-analysis. This cohort of 100 scans were anonymized and randomly coded to maintain blinding to all clinical and invasive date at the time of grading splenic perfusion.

Analysis of splenic perfusion – visual assessment

Splenic perfusion was graded using a simple visual comparison of the signal intensity rise of the splenic tissue on the stress images with a) the rest images of the spleen and b) the stress images of the myocardium. Perfusion was graded as either 'switched-off' (clearly visually lower splenic signal intensity with stress than at rest, and/or lower splenic than myocardial

signal intensity with stress), or 'not switched-off' (visually similar splenic signal intensity at rest and stress, and similar to myocardial signal intensity with stress). In all studies, the observers were also asked to comment on the presence or absence of intestinal peristalsis on the stress images as previous studies[13,14]and our own observations had found that peristalsis is inhibited by adenosine. All scans were assessed independently by 2 mutually-blinded observers from different institutions (CM and DR).

Analysis of splenic perfusion – semi-quantitative assessment

A semi-quantitative analysis was performed using signal intensity curves, analysed using OsiriX, Bernex, Switzerland. For each subject, a region of interest was selected for myocardial and splenic tissue on the stress perfusion images and copied onto the corresponding rest perfusion images. We estimated tissue perfusion using net signal intensity, by subtracting the signal intensity at peak post contrast injection from baseline pre contrast. Net signal intensity was measured in both the rest and stress images, from both the myocardial and splenic tissue. In order to be able to compare the varying magnitudes of signal intensities measured in the scans acquired in different centres, we compared splenic tissue signal intensity at stress with another reference sample identifiable in the same perfusion image. We therefore first calculated splenic:myocardial signal intensity ratio at stress and at rest, and subsequently we calculated stress:rest signal intensity ratios for both myocardial and splenic tissue. For graphs, the RR intervals were extracted from the DICOM datasets.

Validation of splenic switch-off in the CE-MARC dataset

For the anonymized CE-MARC cohort, in addition to splenic perfusion grading, the hemodynamic response to adenosine was graded as 'normal' (>10bpm rise in heart rate) or 'reduced'.[17] Once graded, investigators were unblended to the study data to permit subject categorization using the 3 dichotomous variables available: known true or false negative scan;

spleen switched off or not; and presence or absence of hemodynamic response - producing 8 groups (2x2x2).

Using this data, we were able to address 3 hypotheses;

- Is failed splenic switch-off more common in the false than true negative group?
- Does splenic switch-off track absent hemodynamic response?
- Could splenic switch-off be used to reduce false negatives scans by identifying patients for recall?

Statistical Analyses

Distribution of data was assessed using….. Agreement on classification of splenic perfusion was measured using Cohen's kappa for 2 observers. A kappa score of 0 indicates a purely chance level of agreement, <0.2 may be considered poor agreement and >0.8 very good agreement. Proportions were compared using Fisher's exact test. Analysis of signal intensity ratio differences between perfusion with different pharmacological agents was performed using the Student's unpaired t-test, where $p<0.05$ was taken as significant. The paired t-test was used to compare within subject signal intensity differences in perfusion with stress and rest. Comparison of signal intensities in the true and false negative groups were made using Fisher's exact test…. Values are expressed as mean +- SD unless otherwise stated////

Results

Adequate splenic tissue for analysis of perfusion was seen on the standard myocardial perfusion images in 99% of scans (49/50 adenosine scans from The Heart Hospital, 24/25 dobutamine scans, all regadenoson scans and all CE-MARC adenosine scans).

Splenic perfusion was graded visually by 2 independent blinded observers as 'switch-off' (dark) or 'no switch-off' (bright). There was concordance between the 2 observers in the grading in 47/50 of the adenosine scans from The Heart Hospital, all 25 dobutamine all 25 regadenoson scans, and 95 of the 100 adenosine scans from the CE-MARC trial. Overall the strength of agreement was very good (Cohen's kappa 0.92).

There was splenic switch-off with adenosine in 90% (44 of 49 studies where splenic tissue visible) in the Heart Hospital cohort, Figure 1 and Movie. With regadenason and dobutamine, no splenic switch-off was seen in any of the studies.

Visual comparison of splenic and myocardial perfusion with the 3 stress agents showed that with adenosine stress spleen perfusion was visually clearly attenuated compared to myocardium; with regadenason and dobutamine it was visually unchanged or higher.

At rest, peristalsis was visible in 48 of 50 patients (96%) from Heart hospital. Of these, slowing or arrestation of peristalsis occurred in 43 of 48, 90%. Agreement of grading between observers however was less consistent than for splenic switch-off with adenosine (Cohen's kappa 0.65). Although peristaltic switch-off has the potential to add diagnostic confidence, the inconsistency of baseline observation and lack of agreement meant we did not pursue this sign for this project.

	Stress signal intensity (au)	Rest signal intensity (au)	Comparison
Adenosine (London)	8.12±8.0	33.3±19.0	p<0.0001
Adenosine (Leeds)	306±300	720±280	p<0.0001
Regadenoson	132±55	145±59	p=0.08
Dobutamine	76.3±24		

Table 1 – Splenic signal intensity measured on stress and resting images with 3 different pharmacological stressors, acquired in 4 different units.

Splenic perfusion is significantly reduced compared to at rest, with adenosine but not with regadenoson.

For statistical comparison of the scans acquired in different centers, signal intensity ratios were calculated. All signal intensity ratios were similar between the Leeds and London adenosine scans, and the splenic ratios were significantly lower than with regadenoson (0.32±0.34 versus 0.94±0.24, p<0.0001). To demonstrate that splenic switch-off with adenosine was not the consequence of generalised hypoperfusion or a function of the contrast administration protocol, we calculated myocardial stress:rest signal intensity ratios. Myocardial signal intensity increased with adenosine (stress/ rest signal intensity ratio of >1) but was unchanged with regadenason (1.65±0.64 versus 1.03±0.38, p<0.0001), Figure 3.

Splenic:myocardial signal intensity ratio was significantly lower with adenosine stress than with both dobutamine (0.36±0.4 versus 1.23±0.42, p<0.0001) or regadenoson (1.26±0.53, p<0.0001) stress, Figure 4.

Using the CE-MARC scans, a suboptimal hemodynamic response (<10bpm increase in heart rate) was two fold higher (34% versus 17%, p=0.08) in known false negatives (n=35) compared to true false negative (n=65) adenosine perfusion scans. The rate of failed splenic switch-off however was almost 4 times higher: (34% versus 9%, p<0.0001), Figure 5. Failed splenic switch-off had a relatively high concordance with the presence of suboptimal

hemodynamic responses to the adenosine: 81% of subjects had concordant responses. In the false negative group, 8 subjects out of 35 patients (22%) and 3 of 65 (5%) in the true negative group had neither splenic switch-off nor a hemodynamic response. Figure 5.

Discussion

In this study we identify and describe splenic switch-off; a new sign with a clear potential clinical application in determining stress adequacy during adenosine perfusion CMR. We observed splenic switch-off in 90% of such scans and found it to be straightforward to detect and reproducible with no additional measures required – it just needs to be looked for. Splenic switch-off is not a generic response to pharmacological stress; CMR perfusion sequences acquired following dobutamine and regadenoson show no attenuation of splenic flow. Failure to switch-off splenic perfusion during adenosine perfusion CMR occurs in more than a third of proven false-negative scans – almost four times more commonly than in true negative scans, making it a better marker than haemodynamic response, which is twice as common. Rescanning these subjects who do not exhibit splenic switch-off could potentially reduce false negative perfusion CMR scans by a third. The presence of failed splenic switch-off in 1 in 11 unselected CMR scans suggests that there is a significant rate of under-stress during perfusion CMR, at least in the two centres where it was studied.

In conjunction with its immunological and haematological functions, the spleen also helps to regulate blood volume via extravasation of fluid from the splenic circulation into the lymphatic reservoirs. This is controlled by a variety of neurohormonal mechanisms, and adenosine-mediated splenic vasoconstriction helps to maintain circulatory volume in conditions of shock[18]. Animal studies have shown that despite increased aortic and coronary flow, adenosine administration reduces splenic blood flow by over 75%[12].

Perfusion CMR has now been robustly demonstrated to be a safe, reproducible, sensitive and specific tool in the diagnostic armoury for coronary artery disease. [23,51] Demand for perfusion CMR is growing rapidly in some countries; the consequence of an increasing body of supportive prognostic data[19], evidence of cost-effectiveness[20,21], and a growing recognition of

the need to minimise the radiation exposure associated with alternative techniques[22,23]. Adenosine is the most widely-used pharmacological stressor for perfusion CMR imaging because its proven safety and tolerability[3,17], combined with a wealth of experience from using it within nuclear imaging. Adenosine is a potent coronary vasodilator, which in normal coronary arteries results in significantly increased myocardial blood flow. In coronary arteries with functionally significant flow-limiting lesions however, adenosine elicits regional perfusion defects during first pass perfusion of gadolinium-based contrast agents. In addition to the effects on the coronary vessels, adenosine causes systemic vasodilatation and reflex sympathetic activation, resulting in a mild reduction in systemic blood pressure and a mild increase in heart rate. Unlike with inotropic pharmacological stress agents such as dobutamine where administration is continued until the subject reaches a pre-specified end-point (such as 85% of target heart rate), there is no clear marker of response to adenosine or end-point, and adenosine is simply administered for a fixed time period (generally 3 or 4 minutes). This has led to speculation that there may be a proportion of subjects in whom the adenosine infusion does not cause sufficient coronary vasodilatation to unmask perfusion defects, resulting in a false negative scan result.

Confidence in any diagnostic technique is undermined by false negative results, and although the negative predictive value of adenosine perfusion CMR is at generally better than other techniques used for the diagnosis of coronary artery disease[4,5,24,25], it has remained fairly static over the past decade. The CE-MARC trial provides the largest single-study accrual of false negative CMR perfusion scans to date, and when assessing the potential cause of these scan results, the investigators found that over half of the subjects with false negative scans were likely to have received inadequate pharmacological stress; 34% had an inadequate haemodynamic response to adenosine, and a further 17% had a myocardial perfusion reserve <1.5[26].

Hemodynamic response alone however is insufficient evidence with which to recall and rescan subjects – previous studies have found that around 1 in 6 patients has a blunted haemodynamic response to adenosine[17]. In a large study of subjects undergoing PET scanning (with 140mcg/kg/min of adenosine infused for 6 minutes), despite hyperaemic on measurements of myocardial blood flow, systolic and mean aortic blood pressure remained unchanged.[27] Subjects taking beta-blockers or calcium channel antagonists have also been found to have reduced hemodynamic responses to adenosine and dipyridamole[28,29], and as many subjects undergoing ischaemia testing may be prescribed these medications, hemodynamics may confound assessments of stress response. Within the CE-MARC cohort used in this study, 17% of the *true* negative group had a reduced haemodynamic response to adenosine, in addition to 34% of the false negatives. Splenic perfusion was switched-off in 8/11 of these true negatives and they are therefore likely to have been stressed, meaning that guiding decision-making with hemodynamic response alone may not be helpful.

There is also growing recognition that there is a cohort of patients who may have a reduced haemodynamic response to adenosine as a result of underlying physiology[30], pathology[31] and pharmacology[6], and that the hemodynamic response itself may be a diagnostic and prognostic marker[32,14]. Caffeine is a known potent inhibitor of adenosine, which binds to the receptors in a competitive manner and can abolish the myocardial blood flow heterogeneity induced by adenosine[33]. Subjects are therefore asked to refrain from caffeine consumption for 12 hours prior to the examination, however in practice compliance with this instruction cannot be assessed and some subjects may also be slow metabolisers[6,34]. The biological half-life of caffeine is highly variable between 4.9 hours in healthy people to 26 hours in patients with cirrhosis[35] and 56 hours in those taking fluvoxamine[6]. Further confounding arises from evidence that changes in peripheral heart rate and mean arterial pressure are poor predictors of

changes in myocardial blood flow and coronary vascular resistance[27], meaning that determining stress adequacy from hemodynamic response alone may be misleading.

An ideal protocol would measure left mainstem coronary flow prior to contrast administration during adenosine perfusion CMR to target increases in drug administration, however this is not currently technically feasible in routine clinical scans. Failure of splenic switch-off however offers a simple, reproducible sign to identify patients in whom we risk a false negative result due to pharmacological under-stress, with no requirement for changes to equipment or protocols. Furthermore, measuring splenic flow during adenosine stress to trigger perfusion is likely to be feasible with current technology. We propose that a quick, visual assessment of splenic perfusion should be made both whilst acquiring images during adenosine perfusion CMR examinations, and also by physicians reporting scans, in order to facilitate the detection and potentially the rescanning of inadequately stressed subjects.

Limitations

This study used retrospective data collection, with all scans acquired for clinical purposes or as part of another trial (CE-MARC). It therefore did not aim to compare the performance of the 3 separate pharmacological stress agents for the detection of coronary artery disease, but was designed to assess the feasibility, reproducibility, pharmacology and clinical utility of splenic switch-off as an indicator of inadequate stress in routine clinical adenosine perfusion scans. For simplicity, semi-quantitative measurements of perfusion were made and signal intensity ratios were used to compare scans acquired in the different centers, because of the different protocols, gadolinium administration and equipment used. Objective quantification was performed to corroborate the straightforward visual assessments of splenic perfusion, and therefore this should not detract from the results.

The CE-MARC trial used quantitative coronary angiography (QCA) as the gold standard against which the perfusion CMR and SPECT data were compared. The contemporary gold standard is proposed to be coronary angiography with fractional flow reserve (FFR) measurement, which allows for assessment of the functional significance of coronary lesions. Recent studies[2,36,37] have found that perfusion CMR and MPR also have good diagnostic performance when compared to FFR. It is however possible that false negative rates in the CE-MARC study may be over-estimated using QCA as compared to FFR; subjects with a stenosis of greater than70% that is assessed to be functionally non-obstructive on FFR may have been misclassified as false negatives in the CE-MARC study. If this were the case and subjects with functionally non-obstructive lesions were reclassified from false to true negative, the proportion of false negatives resulting from inadequate pharmacological stress would then increase, thereby increasing the diagnostic performance of the splenic switch-off sign.

Conclusions

Visual assessment of splenic switch-off is a consistent, simple and reproducible finding during adenosine perfusion CMR. Failure of splenic switch-off is an indicator of inadequate pharmacological stress that has the potential to identify patients at risk of false-negative scan results. Rescanning individuals with failure of splenic switch-off would reduce false negative scans by a third, but it may be that up to 1 in 11 of all adenosine perfusion patients are under-stressed. Further work is needed on this important sign.

Disclosures

None declared

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