

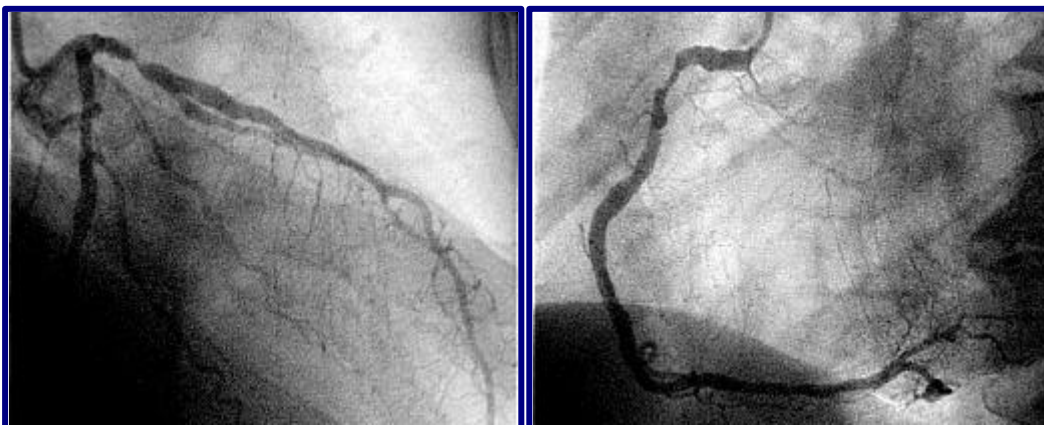
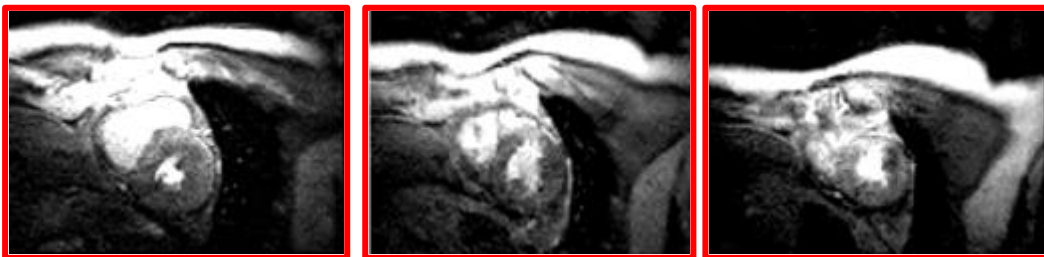
# Perfusion Cookbook

## A Guide to Myocardial Perfusion Analysis During Adenosine Mediated Coronary Vasodilatation for Assessment of Myocardial Perfusion Using Cardiac MR Imaging

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## Purpose

Magnetic resonance perfusion imaging has shown promising results in preliminary studies and first larger patient trials. In principle the occurrence of myocardial perfusion deficits is a very sensitive indicator of ischemia in the presence of significant coronary artery stenoses. Most perfusion defects only occur during stress, such as pharmacological vasodilation. This can be optimally achieved using adenosine or dipyridamole as pharmacological stress agents, both of which proved to be safe and well tolerated.

Techniques currently used in clinical routine such as SPECT and PET have the disadvantage of radiation and low spatial resolution, which prohibits the assessment of subendocardial ischemia. This cookbook provides instructions for the application and performance of perfusion measurements with cardiac magnetic resonance imaging.

## Hard- and Software Requirements

The methodology has been developed for a Gyroscan ACS NT or INTERA 1.5 Tesla (T) whole body system equipped with a 30 mT Master gradient system (slew rate: 150 mT/m/s), using a 5-element cardiac synergy coil. Software: Release 8.1.1 and higher.

## Stress Agents

Pharmakon: Dipyridamole  
concentration: preferably 5 mg/ml  
administration: intravenous

Pharmakon: Adenosine  
concentration: preferably 5 mg/ml  
administration: intravenous

## Mode of Action

Adenosine, an endogenous nucleotide, is a potent vasodilator of most vascular beds, except for hepatic and renal arterioles. It exerts its pharmacological effect through the activation of purine A1 and A2 cell-surface adenosine receptors. The essence of the pharmacological mechanism lies in the inhibition of the slow inward  $Ca^{2+}$  current, thereby reducing calcium uptake, and in the activation of adenylate cyclase through A2 receptors in smooth muscle cells.

Dipyridamole is the prodrug of adenosine and is activated by metabolism in the liver. Thus, vasodilatory capacity depends on individual metabolism rate, usually resulting in a longer half-life, prolonged side effects and reduced vasodilatory capacity in comparison with adenosine.

Both, normal and stenotic coronary arteries are dilated to their maximum using these pharmacons. However, coronary arteries with significant stenosis are already maximally dilated at rest (to allow maximal blood flow and compensate for the stenosis) and cannot be dilated any further. Thus, vasodilation with dipyridamole or adenosine induces an increase of blood flow in myocardial areas supplied by normal coronary arteries ("coronary steal"), whereas no (or only minimal) change is found in areas supplied by stenotic coronary arteries. With adenosine a maximal coronary vasodilation can be achieved safely with an intravenous infusion at a rate of 140  $\mu\text{g}/\text{kg}/\text{min}$ .

## Side Effects

The vasodilatory effect of adenosine may result in a mild-to-moderate reduction in systolic, diastolic and mean arterial blood pressure (< 10 mmHg) with a reflex increase in heart rate. Most patients complain about anginal chest pain. These effects, however, are transient and usually do not require medical intervention.

Since adenosine exerts a direct depressant effect on the SA and AV nodes transient first-, second- and third-degree AV block and sinus bradycardia have been reported in 2.9%, 2.6% and 0.8% of patients. Also, adenosine can cause significant hypotension. Patients with intact baroreceptor reflex are able to maintain blood pressure in response to adenosine by increasing cardiac output and heart rate. Adenosine can also cause a paradoxical increase in systolic and diastolic blood pressure, which mostly develops in individuals with significant left ventricular hypertrophy. These increases are transient and resolve spontaneously. Because adenosine is a respiratory stimulant primarily through activation of carotid body chemoreceptors, intravenous administration showed increases in minute ventilation, reduction in arterial  $PCO_2$  and respiratory alkalosis. Approximately 14% of patients complain of dyspnea and an urge to breathe deeply during adenosine infusion.

## Safety Studies

Because of the above reported adverse effects, a number of studies have been carried out investigating the safety of intravenous adenosine infusions in different diagnostic modalities of cardiac imaging.

So far, there is evidence accumulated in over 10,500 patients studied in thallium radionuclide imaging, echocardiography, SPECT and MRI which shows that pharmacological stress with adenosine presents a safe method of acquiring stress imaging data.

Safety of an adenosine infusion at 140 mcg/kg/min was evaluated during radionuclide imaging of 9,256 consecutive patients. The infusion protocol was completed in 80% of patients, required dose reduction in 13% and was terminated early in 7%. Interpretable imaging studies were obtained in 98.7% of patients, and 0.8% of patients received aminophylline. Minor and well tolerated side effects were reported in 81.1% of patients. There were no deaths, one myocardial infarction, seven episodes of severe bronchospasm and one episode of pulmonary edema. Transient AV node block occurred in 706 patients (first-degree in 256, second-degree in 378 and third-degree in 72) and resolved spontaneously in most patients (n = 508) without alteration in the adenosine infusion. There were no sustained episodes of AV block.

## Contraindications

Adenosine should be used with caution in patients with pre-existing AV block or bundle branch block and should be avoided in patients with high-grade AV block or sinus node dysfunction. Adenosine should be used with caution if a patient is receiving any medications that already depress the sinus node and/or AV node (e.g. beta-blockers, calcium channel blockers, cardiac glycosides).

Adenosine should be discontinued in patients who develop persistent or symptomatic high-grade block or significant drop in systolic blood pressure (>20 mmHg). The drug should be discontinued in case of persistent or symptomatic hypotension.

Also, adenosine should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis and pericardial effusion, stenotic carotid artery disease, cerebrovascular insufficiency and uncorrected hypovolemia.

Adenosine infusion should be exercised with caution in patients with obstructive lung disease not associated with bronchoconstriction (emphysema, bronchitis, etc), and should be avoided in patients with bronchoconstriction or bronchospasm (e.g. asthma). If a patient develops severe respiratory difficulties, adenosine should be immediately discontinued.

Table 1: Dipyridamole / Adenosine stress protocol

Pharmacon	Patient instruction	Stress protocol	Antidote
Dipyridamole (perfusion)	No caffeine (tea, coffee, chocolate, etc.) or medications such as aminophylline or nitrates 24 hours prior to the examination	0.56 mg/kg/min for 4 minutes, maximal effect after approximately 3-4 minutes. (half-life 30 minutes)	Aminophylline 250 mg i.v. slowly injected under ECG monitoring  sublingual nitroglycerine
Adenosine (perfusion)	Same as for dipyridamole	140 µg/kg/min for a maximum of 6 minutes. (half-life 4-10 seconds)	Stop infusion ! (if necessary: aminophylline 250 mg i.v. slowly injected under ECG monitoring)

## Contrast Media for Perfusion

### Drugs:

A gadolinium derivative is used (e.g. Gd-DTPA; gadobenate dimeglumine (Gd-BOPTA); gadodiamide (Gd-DTPA-BMA) etc.) applied as an intravenous bolus. The cookbook protocol is based on extensive experience with Gd-DTPA; correction of dosage regimen is necessary for Gd-derivatives with different relaxivity.

### Dosage for Gd-DTPA:

0.05 mmol/kg bodyweight injected with 4 ml per second. The bolus is followed by a 20 ml saline flush (infusion rate: 4 ml per second) to facilitate a compact bolus passage. We recommend the use of an automatic infusion system ( e.g. Medrad, Spectris® MR injector) for exact dosage and timing.

## Monitoring and Safety

During stress examinations monitoring of the patient within the magnet is mandatory. In general, monitoring during a MR examination requires the same precautions and emergency equipment as any other stress examination. Specific recommendations are listed in table 2. Apart from the known specific contraindications for MR, the drug related contraindications for adenosine and dipyridamole infusion are listed in table 3.

Table 2: Monitoring requirements for adenosine/dipyridamole stress MR imaging

Heart rate and rhythm	Continuously
Blood pressure	Every minute
Pulse oximetry * (for rhythm monitoring)	Continuously
Symptoms	Continuously

\*When the Vector-ECG is used, pulse oximetry is not required.

Table 3: Contraindications for dipyridamole / adenosine

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<ul style="list-style-type: none"> <li>• Myocardial infarction &lt;3 days</li> <li>• Unstable angina pectoris</li> <li>• Severe arterial hypertension</li> <li>• Asthma or severe obstructive pulmonary disease</li> <li>• AV-block &gt;IIa</li> <li>• Caution:               <ul style="list-style-type: none"> <li>autonomic nerve dysfunction</li> <li>stenotic valvular disease</li> <li>cerebrovascular insufficiency</li> <li>any obstructive lung disease</li> <li>comedication with beta-blockers, Ca-antagonists or cardiac glycosides (due to AV / sinus node depression)</li> </ul> </li> </ul>
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Although adverse events are rare, preparation and practice for rapid removal of the patient from the magnet needs to be practiced in addition to a close compliance with the termination criteria (Table 4).

The monitoring of blood pressure, cardiac rhythm and patients' symptoms can either be done by placing standard equipment outside the scanner room connected to the patient with special extensions through a waveguide in the radiofrequency cage, or by using special CMR compatible equipment. A defibrillator and all medications for emergency treatment must be available at the CMR site.

Table 4: Termination criteria

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<ul style="list-style-type: none"> <li>• persistent or symptomatic AV block</li> <li>• significant drop in systolic blood pressure (&gt; 20 mmHg)</li> <li>• persistent or symptomatic hypotension</li> <li>• severe respiratory difficulty</li> </ul>
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## Image Interpretation

### Visual Assessment

Currently, only limited data is available regarding the accuracy of visual assessment and extensive experience is required to reach an acceptable standard. The alteration of the upslope of the myocardial response curve from stress to rest yields the highest difference between ischemic and normal myocardium. This parameter is superior to

maximal signal intensity, which is mainly assessed visually. In our experience a relatively high dose of contrast agent results in improved visual assessment, but often renders semiquantification difficult. Thus, several aspects for visual interpretation need to be taken into account:

Imaging artefacts can obscure (e.g. wraparound) or misleadingly be interpreted (e.g. susceptibility) as perfusion deficits. Thus, training in MR image interpretation together with the interplay of the visual criteria given in table 5 will result in a sufficiently high diagnostic accuracy (own unpublished data showed: sensitivity 89%, specificity 80%).

The main artefacts occurring during the initial passage of the contrast bolus are due to susceptibility at the endocardium-bloodpool (=contrast media) interface, occasionally rendering diagnosis of subendocardial perfusion deficits difficult. Especially the trabeculae of the papillary muscles reaching into the left ventricular cavity are washed with contrast agent and, thus, show almost always susceptibility artefacts. Such findings should not be interpreted as regional ischemic perfusion abnormality.

Visual criteria for left ventricular myocardial perfusion deficits are given in table 5.

## Semiquantification

Most literature has been published on semiquantification, as described briefly: the endo- and epicardial contours of left ventricular myocardium are traced and corrected manually for changes of diaphragmatic position due to breathing or diaphragmatic drift. Care needs to be taken to place the contours on the myocardium and to exclude the left ventricular cavity and the pericardium. The myocardium is then divided into 6 equiangular segments per slice and numbered clockwise beginning with the anterior septal insertion of the right ventricle. An additional region of interest is placed within the cavity of the left ventricle excluding the myocardial segments and the papillary muscles. Images acquired after premature ventricular beats or insufficient cardiac triggering need to be excluded from the analysis to guarantee steady-state conditions. Signal intensity is determined for all dynamics and segments. The upslope of the resulting signal intensity time curve is determined by the use of a linear fit. To correct for possible differences of the input function, the results of the myocardial segments are corrected by dividing the

upslope of each myocardial segment by the upslope of the left ventricular signal intensity curve. Perfusion reserve index is calculated by dividing the results of stress by the results at rest. This approach has yielded sensitivities and specificities of > 90% in selected patient populations. Its value in unselected patients remains to be determined.

Table 5: Criteria for Visual Assessment of Regional Myocardial Perfusion Deficits During First-Pass of Contrast Agent

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- **Signal-intensity Pattern & Location:** Dark regions arising from the subendocardium with usually irregular intramyocardial border or with completely transmural extent are highly suspicious.
  - **Dynamic Myocardial Filling Pattern:** Initially, slow or missing enhancement persistent over a few (2 to 10) dynamics with a consecutive signal intensity increase starting from the defect's epicardial border (epicardial "filling up" of the defect) is typical for regional perfusion abnormalities.
  - **Myocardial Distribution of the Defect:** Evaluate the equatorial slice first, then check whether the suspected perfusion defect can be followed in corresponding segments of the apical or basal slice.
  - **Comparison Stress vs. Rest:** If a regional defect is found in the stress scan, but not in the rest scan, inducible ischemia is confirmed ("dynamic lesion"). Regional persistence of the perfusion deficit shows myocardial scar ("static lesion").

## Quantification

Quantification depends on a number of prerequisites, not fully fulfilled with the current contrast agents such as: linearity between signal intensity and contrast agent concentration or adequate downslope. Most centers have not been able to reproduce methods proposed for quantification. Problems due to background correction, image inhomogeneities, water exchange and magnetization transfer remain unsolved.

## Protocol Overview

To cover 16 segments we use 3 short axis views. However, with this approach the apical segment (segment 17) is neglected (for left ventricular segmentation see "DSMR cookbook). A standardized way to reproducibly plan a short axis view can be found in the application guide.

The study includes the following scans, which are all breathhold bFFE scans (scan duration ranging from 8 to 12 sec.), except for the multistack survey (bFFE, but free breathing patient) and the TFE-EPI perfusion scan:

- (1) multistack survey (bFFE)
- (2) single-angulated view
- (3) double-angulated view
- (4) wall motion scan short axis (3 slices)
- (5) 4-chamber view
- (6) 2-chamber view
- (7) Perfusion scan (3 slices)

The perfusion scan will be performed during stress and at rest (after an equilibration time  $\geq 15$  min after the first bolus injection).

## Step by Step Protocol

### Patient Preparation

It is of special importance to explain not only the course of the examination to the patient but also the breathhold procedure. Generally the breathhold should be performed during endexpiration to ensure reproducible slice geometry.

The perfusion scan consists of two breathhold periods. The first is a short one (about 10-12 seconds, baseline acquisition of myocardial intensity), then the patient is asked to inhale and exhale once and hold breath as long as possible. Before starting this breathhold-command the contrast bolus is administered. The patient should stop breathing for at least 25-30 seconds resulting in a fixed slice geometry during the first-pass of the contrast agent; in case the patient cannot hold his breath throughout the whole scan: ask the patient to inhale and exhale once and hold breath again.

Put venous line ( $\geq 18$  gauge) in cubital vein with two connections: one for adenosine, one for contrast media.

Monitor blood pressure and heart frequency on contralateral arm.

### Scan Procedure:

#### Scan 1 (Multistack survey, CSC [cardiac synergy coil] all elements):

Look at the images and check if the coil is positioned well.

#### Scan 2 (single-angulated view):

Define the plane on transversal slices parallel to the septum through the apex of the left ventricle and the coaptation point of the mitral valve.

#### Scan 3 (Repeat Scan 2, bFFE):

Flip the orientation ( $90^\circ$ ) and adjust the plane on the first RAO through the apex and the middle of the mitral valve to get a second long axis view (nearly 4 chamber view). This slice orientation helps to prevent any angulation errors while planning the short axis views.

#### Scan 4 (bFFE):

Make use of the double-angulated image to define 3 slices perpendicular to the long axis of the heart representing the short axis geometry.

Note: Under stress conditions even the normal heart experiences a change in its basal-to-apex dimensions due to rotational deformation. To avoid visualization of the left ventricular outflow tract as well as to ensure sufficient imaging of the left ventricular cavity (esp. critical is the apical slice), we recommend to perform the planning on the endsystolic images: divide the distance from the apical epicardial border to the mitral valve plane in 5 equal parts. Then, distribute the 3 short axes equally within the inner three-fifth of the distance with adaptation of slice gap.

#### Scan 5 (bFFE):

Plan the 4-chamber view on the equatorial short axis view, the stack should be aligned through the apex of the right ventricle and the papillary muscle.

#### Scan 6 (bFFE):

Plan the 2-chamber view on the previously acquired 4-chamber view by just switching the slice orientation and adjust the angulation (through the left ventricular apex and the coaptation point of the mitral valve).

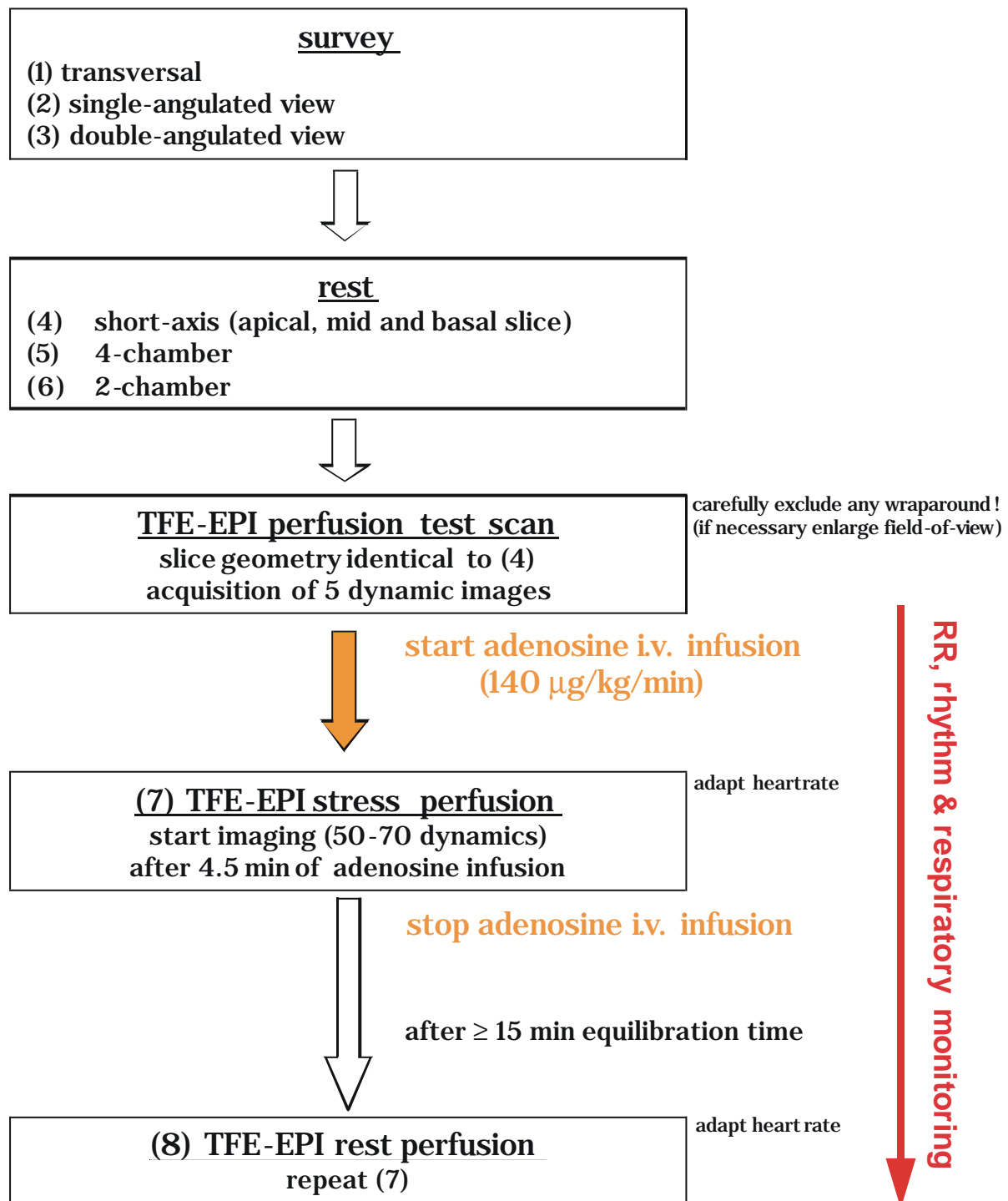
#### Scan 7: TFE-EPI stress perfusion

The perfusion scan is performed with an orientation identical to the short axis cine previously acquired (scan 4). Wraparound has to be avoided carefully! We recommend to perform a TFE-EPI prior to the start of the adenosine infusion (e.g. 5 dynamics) with a breathhold command if necessary enlarge the field-of-view (results in decreasing resolution).

#### Scan 8:

Repeat scan 7 at rest after  $\geq 15$  min delay.

## Flow chart 1: Adenosine Stress MR Perfusion Imaging



## Survey MST bFFE

Geometry	
Coil selection/ch. connection	Syn-Cardiac/12345
FOV(mm)/RFOV	490/90%
Matrix Scan/Reconstruction/Scan%	192/256/70
Slices/thickness(mm)/gap	21/9/-1
Stacks/Type	3/parallel
Contrast	
ScanMode/Technique/Fast Imaging	M2D/FFE/none
Partial Echo	no
TE(ms)/Flip(deg)/TR(ms)	shortest/55/shortest
Half Scan	no
Water fat shift	min
Contrast enhancement/Shim	balanced/auto
Motion	
Cardiac synchronization/device	gate/ECG
Card. Freq./RR%/#Phase	70/10,10/1
Gate delay (ms)	300
Gate width	longest
Flow Comp./NSA	no/1
Dyn/Angio	
Angio/Q.Flow/Dyn. Study	no/no/no
Post Processing	
Recon Mode	real time

## Single - and double - angulated survey

Geometry	
Coil selection/ch. Connection	Syn-Cardiac/12345
FOV(mm)/RFOV	400/80%
Matrix Scan/Reconstruction/Scan%	256/256/60
Slices/thickness(mm)/gap	1/8/-
Stacks/Type	1/parallel
SENSE*/p reduction	yes/2
Contrast	
Scan Mode/Technique/Fast Imaging	M2D/FFE/none
Partial Echo	no
TE(ms)/Flip(deg)/TR(ms)	shortest/55/shortest
Half Scan	no
Water fat shift	min
Contrast enhancement/Shim	balanced/auto
Motion	
Cardiac synchronization/device	gate/ECG
Card. Freq./RR%/ #Phase	70/10,10/20
Phase interval	longest
Gate delay (ms)	shortest
Gate width	longest
Respiratory compensation/slices per bh	breath hold/1
Flow Comp./NSA	no/1
Dyn/Angio	
Angio/Q.Flow/Dyn. Study	no/no/no
Post Processing	
Recon Mode	real time

\*alternative: half scan = yes

## Cine SA/2CH/4CH bFFE

Geometry	
Coil selection/ch. Connection	Syn-Cardiac/12345
FOV(mm)/RFOV	350/100%
Matrix Scan/Reconstruction/Scan%	208/256/100
Slices/thickness(mm)/gap	1-3/8/user def
Stacks/Type	1/parallel
SENSE*/p reduction	yes/2
Contrast	
Scan Mode/Technique/Fast Imaging	M2D/FFE/none
Partial Echo	no
TE(ms)/Flip(deg)/TR(ms)	shortest/55/shortest
Half Scan	no
Water fat shift	min
Contrast enhancement/Shim	balanced/volume
Motion	
Cardiac synchronization/device	gate/ECG
Card. Freq./RR%/ #Phase	70/10,10/20
Phase interval	longest
Gate delay (ms)	shortest
Gate width	longest
Respiratory comp./slices per bh	breath hold/1
Flow Comp./NSA	no/1
Dyn/Angio	
Angio/Q.Flow/Dyn. Study	no/no/no
Post Processing	
Recon Mode	real time
Measured Voxel Size/mm	1.7 x 1.7 x 8

\*alternative: half scan = yes

## Perfusion TFE -EPI

Geometry	
Coil selection/ch. Connection	Syn-Cardiac/12345
FOV(mm)/RFOV	350/70
Matrix Scan/Reconstruction/Scan%	128/128/100
Slices/thickness(mm)/gap	3/8/user def
Stacks/Type	1/parallel
Contrast	
Scan Mode/Technique/Fast Imaging	MS/FFE/TF-EPI
Partial Echo	no
TE(ms)/Flip(deg)/TR(ms)	shortest/30/shortest
Half Scan/factor	yes/0.6
EPI factor	11
Shot mode	single shot
Water fat shift	min
TFE prepulse/before each shot/delay (ms)	saturate/yes/130
Contrast enhancement/Shim	T1/no
Motion	
Cardiac synchronization/device	trigger/ECG
Card. Freq./RR%/#Phase	70/10,10/1
Trigger delay (ms)	as long as possible
Flow Comp./NSA	yes/1
Dyn/Angio	
Angio/Q.Flow/Dyn. Study	no/no/yes
Dyn scans/dyn scan times	70/shortest
Post Processing	
Recon Mode	real time
Measured Voxel Size/mm	2.7 x 2.7 x 8
<b>CAVE (!):</b> Check Info Page	
TFE shot intervall (beats)	<b>1 (!),</b> (if not, adjust trigger delay !!!)

**This cookbook has been assembled from the knowledge available at the time of writing. The authors cannot take liability for dose regimen, infusion schemes, etc. If you find any errors or would like to suggest any improvements, please let us know at [eike.nagel@dhzb.de](mailto:eike.nagel@dhzb.de) or [info@cmr-academy.com](mailto:info@cmr-academy.com).**