

## Stress MRI for Evaluation of Coronary Artery Disease

### Types of Stress MR Imaging

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Disclosure: Gd-based contrast media for cardiac perfusion are off-label use in the United States and some European countries.

#### Detection of hemodynamically significant coronary stenoses

In principle, hemodynamically significant stenoses can be detected by provoking ischemia, which then leads to hypokinesia. Hypokinetic regions will then be detected by CMR imaging. Alternatively, a vasodilator can be administered, which causes hyperaemia in tissue subtended by non-stenotic arteries, but hypoperfusion will occur in territories subtended by hemodynamically stenosed coronary arteries (see figure 1).

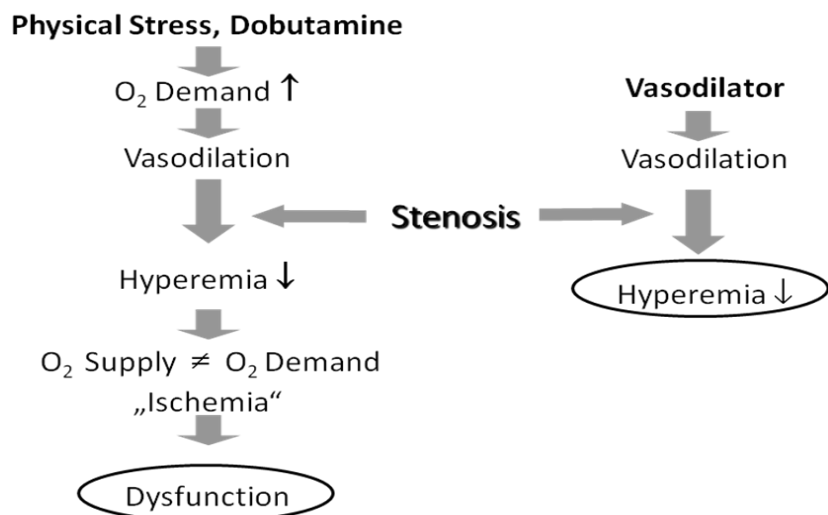


Figure 1: Principles of stenoses detection by CMR

Myocardial ischemia can be provoked by physical stress (e.g. treadmill) or by inotropic stimulation (e.g. dobutamine IV). As both approaches are aimed at provoking ischemia, also side effects are expected to occur such as angina, dyspnea, arrhythmias, blood pressure increase (or decrease in case of severe ischemia).<sup>1</sup>

Conversely, induction of hyperaemia is very unlikely to cause ischemia by a steal effect. At least in animal models, it could be shown, that only severe stenoses of epicardial coronary arteries (about 90% diameter reduction) will cause ischemia in the subendocardial layer.<sup>2</sup> This fact also explains why vasodilators performed poor in stress tests looking at dysfunction during vasodilation.

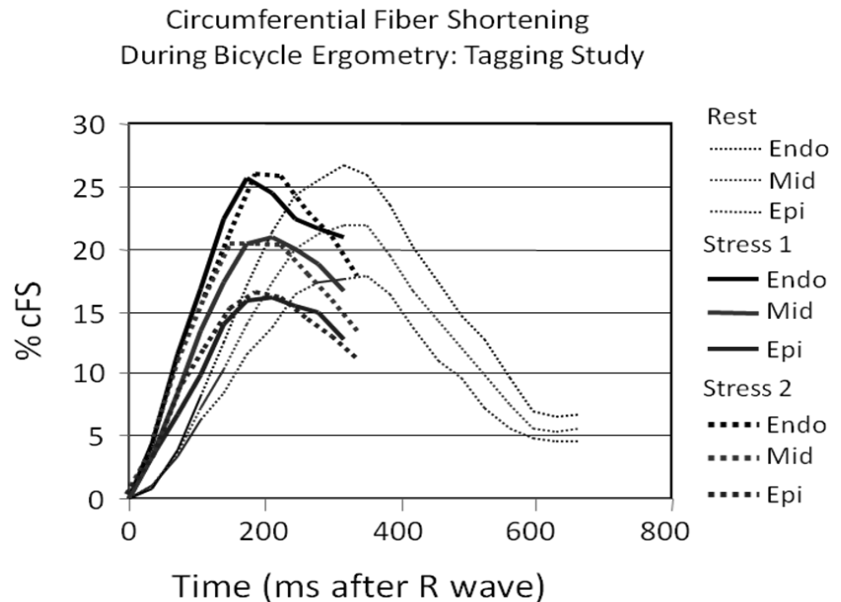
#### Inotropic Stress Test

##### Protocol for inotropic stimulation:

The protocol for pharmacological stress test by dobutamine is following mainly that for stress echocardiography starting with a baseline study, followed by imaging the 17 segments of the heart every 3 minutes during increasing doses of dobutamine of 10 µg/kg; 20 µg/kg; 30 µg/kg; and 40 µg/kg, followed by atropine (at a maximum of 2mg IV) in case that maximum heart rate (220 bpm - age) was not reached (for more details, see also “CMR-Update”<sup>3</sup>).

It is important to note, that ischemia will be detected by this approach through recognition of hypo/akinesia. The myocardial response is unequivocal, i.e. ischemia will always manifest as hypo/akinesia. An example is given in figure 2. In this context, it should be noted, that in hibernating myocardium, dobutamine stimulation can first provoke an increase in kinetics (= recruitment of contractility), and only later during the test hypokinesia does occur (bi-phasic response).

Figure 2  
Circumferential fiber shortening (cFS) at the midventricular level in a normal volunteer during physical stress measured twice each at different myocardial layers. Note, the velocity of shortening increases vs rest, rather than the amplitude of response.



**Perfusion Test**

**Protocol for perfusion stimulation:**

The protocol for pharmacological hyperaemia testing by adenosine is following mainly that for single photon emission computed tomography (SPECT) with a dose of 0.14mg/kg/min for 3 min. This dose induces maximum hyperemia and is safe (1 myocardial infarction in >9000 examinations, no death).<sup>4</sup> Alternatively, dipyridamole can be administered at a dose of 0.56mg/kg for 4 min. For more details, see also "CMR-Update".<sup>3</sup> A novel selective A<sub>2A</sub> agonist, regadenoson, was recently approved for pharmacologic stress testing in the US. This drug can be injected as a single bolus and first studies report a similar diagnostic accuracy as for adenosine (in the setting of nuclear scintigraphy) and a high safety.<sup>5</sup>

**Influence of Imaging Parameters on Signal Response: In-vitro Study**

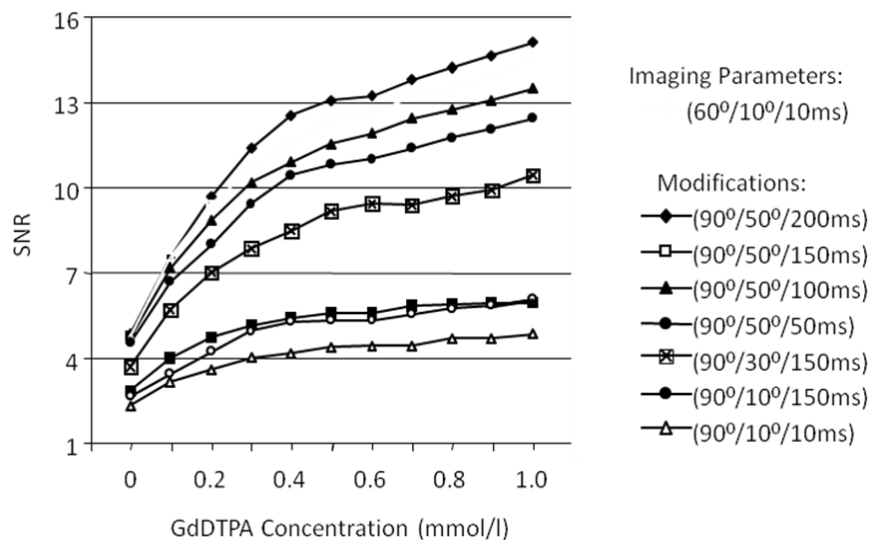


Figure 3  
The signal response of a perfusion sequence is dependent upon imaging parameters.

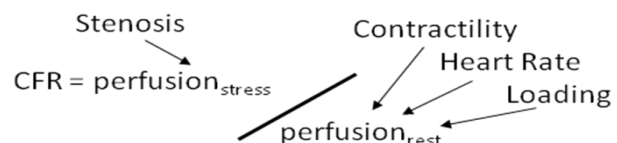
For perfusion imaging, the myocardial response during a first-pass acquisition is not only dependent upon the presence of a significant stenosis (= changes in perfusion), i.e. the response is not unequivocal. The signal response in the myocardium does not only depend upon perfusion (typically a lower signal increase during first-pass of a Gd-chelate is observed in the presence of hypoperfusion), but also upon the type of pulse sequence, the imaging parameters, water exchange (between intravascular and extravascular space), the type and dose (and injection speed) of the contrast medium, degree of leakage of contrast medium (e.g. during ischemia), the input function, and others.

### Stress-only versus stress-rest protocol

An open question remains as to the protocol being either a stress-only protocol or a stress-rest protocol. In the stress-rest protocol, coronary flow reserve (CFR) is calculated by dividing hyperemic stress perfusion by resting perfusion. This approach therefore, requires parameters which must be linearly related to perfusion over a wide range of flow values covering resting flow (approximately 1ml/min/g) and hyperemic flow (as high as 4-5ml/min/g). Since the upslope is non-linearly related with high flow rates<sup>6,7</sup>, this parameter appears suboptimal for a CFR approach and fully quantitative perfusion measurements (in ml/min/g) might therefore be required for the CFR approach.

Applying a stress-only protocol appears advantages, since perfusion in myocardial regions supplied by hemodynamically relevant stenoses (blunting hyperemic flow response with resulting perfusion of approximately 1ml/min/g) is compared with normally perfused, i.e. hyperemic myocardium (allowing perfusion in the range of 2-5ml/min/g). Thus, a stress-only protocol differentiates low perfusion (approximately 1ml/min/g or lower in the case of steal) with very high flows, rendering this approach less sensitive for non-linearity. In addition, the CFR approach also incorporates the measurement of a baseline flow (=resting flow) which is not uncoupled from oxygen demand.<sup>8</sup> Ideally, the factors determining oxygen demand, and thus, flow should be controlled to yield robust CFR normal values (see Figure 4).

Figure 4:  
Factors that influence resting flow and thus, CFR determination (modified according reference<sup>8</sup>)



A stress-only protocol in a multicenter design yielded high sensitivities and specificities of 93% and 75%, respectively, for pooled data of groups with 0.1 and 0.15mmol/kg of contrast medium<sup>9</sup>. In the MR-IMPACT, stress data were analyzed and yielded an excellent diagnostic performance (area under the ROC curve: 0.86).<sup>10</sup> To our knowledge, no multicenter trials are available so far assessing the CFR approach for detection of coronary artery disease.

### Integration of ischemia/perfusion and viability testing

In a stress-only approach, a combination with delayed enhancement MR imaging for detection of scar tissue<sup>11,12</sup> appears reasonable in analogy to the stress-injection and rest-injection for redistribution in SPECT imaging. It should be mentioned here, that both, rest injections of CMR and SPECT exploit contrast medium redistribution for viability/scar discrimination (the MR contrast medium redistribute into the interstitial space of scar tissue, while radioactive tracer redistributes into viable myocytes resulting in high signal and "cold spots" for scar tissue, respectively). More information regarding principles and mechanisms of ischemia and viability imaging are available under reference.<sup>13</sup>

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