Hyperoxia Exacerbates Myocardial Ischemia in the Presence of Acute Coronary Artery Stenosis in Swine

Dominik P. Guensch, MD; Kady Fischer, BHSc; Nancy Shie, BSc; Julie Lebel, RLAT; Matthias G. Friedrich, MD

Background—Current guidelines limit the use of high oxygen tension after return of spontaneous circulation after cardiac arrest, focusing on neurological outcome and mortality. Little is known about the impact of hyperoxia on the ischemic heart. Oxygen is frequently administered and is generally expected to be beneficial. This study seeks to assess the effects of hyperoxia on myocardia oxygenation in the presence of severe coronary artery stenosis in swine.

Methods and Results—In 22 healthy pigs, we surgically attached a magnetic resonance compatible flow probe to the left anterior descending coronary artery (LAD). In 11 pigs, a hydraulic occluder was inflated distal to the flow probe. After increasing PaO₂ to >300 mmHg, LAD flow decreased in all animals. In 8 stenosed animals with a mean fractional flow reserve of 0.64±0.02, hyperoxia resulted in a significant decrease of myocardial signal intensity in oxygenation-sensitive cardiovascular magnetic resonance images of the midapical segments of the LAD territory. This was not seen in remote myocardium or in the other 8 healthy animals. The decreased signal intensity was accompanied by a decrease in circumferential strain in the same segments. Furthermore, ejection fraction, cardiac output, and oxygen extraction ratio declined in these animals. Changing PaCO₂ levels did not have a significant effect on any of the parameters; however, hypercapnia seemed to nonsignificantly attenuate the hyperoxia-induced changes.

Conclusions—Ventilation-induced hyperoxia may decrease myocardial oxygenation and lead to ischemia in myocardium subject to severe coronary artery stenosis. (Circ Cardiovasc Interv. 2015;8:e002928. DOI: 10.1161/CIRCINTERVENTIONS.115.002928.)

Key Words: coronary stenosis ▪ hyperoxia ▪ ischemia ▪ magnetic resonance imaging ▪ oxygen ▪ swine

Exogenous oxygen administration, resulting in high arterial oxygen tension, is frequently applied in medical care.¹ Importantly, oxygen and carbon dioxide both have vasoactive properties. Although increased CO₂ levels have vasodilative properties in cerebral and coronary arteries,²,³ high oxygen tension may have vasoconstricting effects on coronary arteries.⁴ If such vasoconstriction would result in a net reduction of blood flow in the territory of a severely stenotic coronary artery, tissue oxygenation may drop. Little, however, is known on whether hyperoxia can exacerbate or induce myocardial ischemia in myocardium exposed to severe coronary artery stenosis. The current American College of Cardiology/American Heart Association (AHA) resuscitation guidelines limit the use of excessively high inspiratory oxygen concentrations in postcardiac arrest care (class I, level of evidence C) after return of spontaneous circulation (ROSC).⁵ Yet, these recommendations are mainly based on animal studies focusing on neurological pathophysiology and outcome.⁶,⁷ Similar studies have not been published related to myocardial ischemia; yet large retrospective multicenter trials have suggested that hyperoxia may increase patient mortality after cardiac arrest with ROSC.⁸

Oxygenation-sensitive cardiovascular magnetic resonance (OS-CMR) imaging detects myocardial oxygenation changes by exploiting the paramagnetic properties of deoxyhemoglobin. Reduced hemoglobin saturation, reduced myocardial blood flow, and increased oxygen extraction of the myocardium, result in a higher deoxyhemoglobin fraction in the tissue, which will reduce signal intensity (SI) in oxygenation-sensitive sequences.⁹ Thus, OS-CMR is a method that can detect myocardial ischemia on a tissue level in vivo. It has been shown that it can detect changes in myocardial oxygenation triggered by systemic changes of blood gases, that is, oxygen and carbon dioxide.¹⁰¹¹

The purpose of this study was to investigate the effect of hyperoxia on myocardial oxygenation and myocardial
Hyperoxia has known effects on coronary vasomotor tone.

WHAT THE STUDY ADDS

- Hyperoxia decreases coronary flow in a swine model of acute significant coronary artery stenosis and does not compensate for coronary vasoconstriction.
- Hyperoxia results in a decrease in myocardial oxygenation and regional wall motion in the territory of the acute significant coronary stenosis.
- Hypercapnia may reverse this effect.

Fractional Flow Reserve–Guided Stenosis of the LAD

All animals received a bolus of 5000 U heparin intravenously. Eleven animals served as controls, while in 11 animals a perivascular hydraulic occluder (In Vivo Metric, Healdsburg, CA) was mounted around the LAD distal to the flow probe. Hyperemia was induced with 140 µg/kg per minute adenosine intravenously, and fractional flow reserve (FFR) was measured with a pressure guidewire (St. Jude Medical, St. Paul, MN). The occluder was then inflated to yield an FFR value of <0.75 during maximal hyperemia. An FFR of 1.0 was assigned to the control animals. In all animals, a quantitative coronary angiography was performed after the preparation in a single plane view to confirm normal coronaries in the control animals and the degree of stenosis in the stenosis group.

CMR Protocol

The animals were transferred to the magnetic resonance imaging (MRI) suite and placed in recumbent position. After baseline scans, the FiO2 was set to 1.0 and ventilation rate was adjusted to target PaO2 levels of 30, 40, and 50 mmHg, respectively. At each level, arterial and coronary sinus blood gases, heart rate, arterial blood pressure, SpO2, changes in LAD blood flow, left ventricular function parameters, and oxygenation-sensitive (OS)-CMR images were recorded. The myocardial oxygen extraction ratio (O2er) was calculated from the oxygen content of the arterial (CaO2) and coronary sinus (CcsO2) blood: O2er=(CaO2−CcsO2)/CaO2. All parameters were compared with the baseline of PaO2=100 mmHg and PaCO2=40 mmHg. Blood gas levels were set in random order.

Images were acquired with a clinical 3T MRI system (MAGNETOM Skyra 3T; Siemens Healthcare, Erlangen, Germany) using an 18-channel cardiac phased array coil. LV function was imaged using an ECG-gated balanced steady-state free precession sequence (echo time], 1.43 ms; repetition time, 3.3 ms; flip angle, 65°; voxel dimensions, 1.6x1.6x6.0 mm; and bandwidth, 962 Hz), covering the entire left ventricle with a short-axis stack. OS-CMR images were acquired in 2 short-axis slices (midventricular and midapical) using an ECG triggered steady-state free precession sequence (echo time/repetition time, 1.70 ms/3.14 ms; flip angle, 35°; voxel dimensions, 2.0x2.0x10.0 mm; and bandwidth, 1302 Hz).

Statistical Analysis

Data are expressed as mean±SEM. Continuous variables were assessed for normal distribution with the D’Agostino–Pearson test. Paired t tests or repeated measures ANOVA were used to compare data from baseline, and independent t tests compared data between groups. In the case of multiple analyses, repeated measures ANOVA’s or 2-way mixed effects models were used to compare results both within and between groups, with following post hoc tests. If the data were not normally distributed a Mann–Whitney or a Wilcoxon matched-pairs signed-rank test was performed. Associations between ΔS1 FFR, O2er, and coronary flow were assessed with Pearson correlation. Tests were performed with GraphPad Prism version 6.0 for Mac (GraphPad Software, La Jolla, CA) and SPSS version 21 (SPSS IBM, New York, NY). Results were considered statistically significant if the P<0.05.

This study was conducted in accordance with the Guide to the Care and Use of Experimental Animals by the Canadian Council on Animal Care and approved by the local Animal Care and Use Board.

Results

In the group of healthy pigs, 2 animals had to be excluded: one died after surgical complications, whereas 2 animals died later during the MRI scans because of refractory cardiovascular instability. Three animals died by stenosis-induced ischemia, resulting in 8 animals in both groups.
Severity of Stenosis

The inflation of the perivascular occluder around the LAD resulted in a mean FFR of 0.64±0.02 during maximal hyperemia and a reduction in vessel diameter of 62.9±4.9% versus 7.1±2.7% (P<0.001) in the control animals.

Myocardial Blood Flow

There was no significant difference in baseline LAD flow between the stenosis and control animals. Induced hyperoxia, however, resulted in a significant decrease in LAD blood flow in the stenosis animals by −24.0±4.5%, −14.8±2.0%, and −13.1±5.1% for hypo-, normo-, and hypercapnic hyperoxia, respectively (P<0.05). In control animals, hyperoxia only decreased flow under hypocapnia (−13.3±5.0%; P<0.05) and normocapnia (−12.7±2.3%; P<0.01), whereas hypercapnia neutralized this effect (+2.2±5.5%, n.s.). Although increasing PaCO2 levels seemed to attenuate the hyperoxia-capnia neutralized this effect (+2.2±5.5%, n.s.). Although increasing PaCO2 levels (−10.6±2.3%; hyperoxia (−6.7±1.1%; P<0.05) during hyperoxic hypo- and normocapnia (−12.7±2.3%; hyperoxia (−10.6±2.3%; P<0.01) compared with baseline, while there was no change in the control animals.

Myocardial Oxygen Extraction Ratio

Before the experimental procedure in the MRI, baseline myocardial oxygen extraction ratio was higher in the ischemic animals (59±4%) versus healthy animals (47±3%; P<0.05) at physiological blood gas levels (PaO2=100 mm Hg, PaCO2=40 mm Hg). In the stenosis group, myocardial oxygen extraction ratio was decreased during normocapnic hyperoxia (−6.7±1.1%; P<0.05) and hypercapnic hyperoxia (−10.6±2.3%; P<0.01) compared with baseline, while there was no change in the control animals.

Oxygenation-Sensitive Cardiovascular Magnetic Resonance

For predefined criteria, 9.7% of all myocardial segments had to be excluded because of susceptibility artifacts in the inferolateral wall (5.5% segments of healthy and 14.0% of stenosis animals).

Inducing blood gas changes yielded no global signal intensity (differences in myocardial oxygenation in either slice.

Changes in the LAD perfusion territory in the midapical SAX slice are shown in Table 1. Figure 1 shows the change in SI after induction of hyperoxia from baseline in a healthy and a stenosed animal, accompanied with the changes in myocardial strain. Although increased supranormal oxygen tension resulted in increased SI in healthy animals, hyperoxia resulted in an SI decrease during hypocapnia and normocapnia (Table 1; Figure 2). The SI increases were attenuated in stenosis animals compared with the control group during hypercapnic hyperoxia. There was no difference in myocardial SI in the LAD territories in the midventricular slice.

Function Parameters

In stenosis animals, left ventricular ejection fraction did not differ at baseline, but was significantly reduced after induction of hypo- and normocapnic hyperoxia (Table 2; P<0.05) when compared with healthy animals. Cardiac output in ischemic animals was initially lower at baseline, and decreased further during hyperoxic hypo- and normocapnia (P<0.05).

Circumferential strain was significantly attenuated from baseline values in the LAD territory of the ischemic animals (Figure 3) at a PaO2 of 300 mm Hg for 30 mm Hg PaCO2 (−21.35±10.52; P<0.05) and 40 mm Hg PaCO2 (−18.24±9.72; P<0.05), whereas a PaCO2 of 50 mm Hg further enforced a trend for a reduction in strain (−18.43±9.66; P=0.055). Furthermore, global strain was −16.60±7.70% reduced during hypocapnic hyperoxia. No change in myocardial strain was seen for the remote myocardium or the LAD perfusion territory in healthy animals during any hyperoxic level.

Relationship to Oxygenation Changes

The changes in myocardial SI in the LAD territory of the midapical slice showed a strong association with the measured FFR of the coronary artery stenosis for all blood gas levels (hypocapnic hyperoxia: R=0.53, normocapnic hyperoxia: R=0.58, hypercapnic hyperoxia: R=0.60; P<0.05). In addition, changes in flow at supranormal hyperoxia were also correlated with changes in OS-SI in the LAD territory (R=0.5; P<0.05). Otherwise, no significant correlations were observed with O2 or flow to other levels.

These correlations were not seen in the midventricular slice, more proximal to the stenosis.

Discussion

Our study provides evidence that hyperoxia may worsen myocardial ischemia in severe coronary artery stenosis, accompanied by ventricular dysfunction.

Before the 2010 revision of the American College of Cardiology/AHA guidelines, supplementation of oxygen for patients with acute coronary syndrome was considered beneficial, based on previous findings that supplemental oxygen may decrease myocardial injury.12,13 The studies, dating from the 1970s, however, were not standardized, randomized, or controlled. In 1976, Rawles and Kenmure4 performed a randomized double-blinded controlled study and showed that oxygen therapy was associated with higher aspartate aminotransferase levels post infarct, indicating more severe myocardial injury, and found no benefit with respect to mortality.

Table 1. Changes in Myocardial Signal Intensity From Baseline

<table>
<thead>
<tr>
<th>Level</th>
<th>Control</th>
<th>Stenosis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midventricular slice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300/30</td>
<td>−2.0±2.0</td>
<td>0.1±1.1</td>
<td>0.31</td>
</tr>
<tr>
<td>300/40</td>
<td>2.2±2.0</td>
<td>−0.3±1.4</td>
<td>0.35</td>
</tr>
<tr>
<td>300/50</td>
<td>0.7±1.3</td>
<td>0.1±1.6</td>
<td>0.76</td>
</tr>
<tr>
<td>Midapical slice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300/30</td>
<td>1.9±1.7%</td>
<td>−2.8±0.9%</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>300/40</td>
<td>2.6±1.3%</td>
<td>−2.0±1.0%</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>300/50</td>
<td>4.0±1.2%</td>
<td>+0.2±0.7%</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

Changes in myocardial signal intensity (%) from baseline (PaO2=100 mm Hg, PaCO2=40 mm Hg) in the midventricular and midapical slice in the left anterior descending coronary artery territory. Changes in signal intensity between control and stenosis animal for all hyperoxic levels are different (P<0.05), whereas none of the changes are different in the midventricular slice. Levels depicted as PaO2 (mm Hg)/PaCO2 (mm Hg), mean±SEM.
Although not significant, the data even suggested that mortality may be higher in the oxygen than in the control group (13.3% versus 3.9%). In 1971, Loeb et al observed in a clinical study in 31 patients with acute noncomplicated myocardial infarction, that treatment with 6 L/min oxygen was associated with a higher mean arterial pressure, a lower cardiac index and, in 7 patients, an increase in LV end diastolic pressure. Nevertheless, the authors suggested that oxygen should be administered in these patients because of a high incidence of concurrent hypoxemia.

Literature shows that oxygen is still administered in 80% of cases with acute myocardial infarction and >50% of health professionals consider it to reduce mortality. McNulty et al showed that breathing supplemental oxygen for 15 minutes with a mask increases coronary vascular resistance by 40% and decreases Doppler flow velocity by 20% and coronary blood flow by 30% in patients undergoing cardiac catheterization.

Potential mechanisms that lead to hyperoxic coronary vasoconstriction have been outlined by Moradkhan and Sinoway. Nitric oxide that relaxes smooth muscle cells in the arterioles act as a scavenger for reactive oxygen species during hyperoxia. This results in a reduced bioavailability of nitric oxide and to vasoconstriction. An animal study also suggested the presence L-type calcium channels on vascular smooth muscle cells, which contribute to blood flow control in an oxygen-sensitive manner. Metabolic demands are also controlled by ATP-gated potassium channels. Hypoxia leads to a drop in ATP levels in the cells. These potassium channels open if the ATP concentration falls, resulting in increased tissue perfusion.

Hyperoxia, however, was found to reverse that effect, down-regulating flow in the coronary arteries. Furthermore, isolated cardiomyocytes were found to convert angiotensin I to angiotensin II during a hyperoxic stimulus, which could potentially release the vasoconstrictor endothelin-1 levels.

The mounting evidence of reduction of coronary blood flow during hyperoxia led to concern about the safety of oxygen.
A meta-analysis of 6 studies in 665 patients by Caldeira et al.24 showed that oxygen therapy for acute myocardial infarction may increase the risk of death by 16%. Moradkhan and Sinoway1 stated that hyperoxia is not perceived to be detrimental by medical staff because of conflicting data and a lack of randomized, blinded, and controlled studies.

The current AHA resuscitation 2010 guidelines do not limit the use of oxygen during cardiac arrest but in patients with ROSC (class I, level of evidence C).5 These recommendations are based on neurological studies where hyperoxia as a part of the ischemia/reperfusion injury exacerbated neurological outcome.25,26 whereas normoxic ventilation seems to attenuate that effect.6,7

A retrospective multicenter cohort study in the United States included 6326 intensive care unit patients with ROSC in 3 groups: hypoxia (<60 mmHg PaO2), normoxia (60–300 mmHg), and hyperoxia (>300 mmHg).8 The group found that hyperoxia (63% mortality versus 45% in normoxia and 57% in the hypoxia group) was independently associated with increased in-hospital mortality, with an odds ratio for hyperoxia (63% mortality versus 45% in normoxia and 45% in hypoxia) of 0.8 versus 18.3% in the group with a FiO2 of only 0.3 in this randomized trial follow-up.

Most of the referenced studies assessed changes in neurological outcome after ROSC or death. However, it is not clear how many of these deaths were because of a hyperoxic-induced aggravation of myocardial ischemia. There is also invasive data on changes of coronary resistance and myocardial blood flow.4 However, these studies cannot assess the impact on the myocardium on a tissue level as the increase in arterial oxygen content (CaO2) can counterbalance the reduction in myocardial blood flow.

OS-CMR can detect the changes in myocardial oxygenation in vivo using the paramagnetic properties of deoxygenated hemoglobin as an inherent contrast.9 Changes in delivery or myocardial oxygen demand such as myocardial blood flow, hemoglobin saturation, myocardial workload, and oxygen extraction all factor into changes in OS-SI. Myocardial oxygenation depends on the balance of oxygen delivery and demand. Delivery is determined by vascular density, blood flow, hemoglobin concentration, and hemoglobin oxygenation, whereas demand is reflected by the myocardial workload. If oxygen delivery does not meet the metabolic requirements, the relative concentration of deoxygenated hemoglobin in postcapillary venules increases, while that of oxyhemoglobin decreases. The increase in deoxyhemoglobin leads to a decrease of SI in oxygenation-sensitive MRI. Thus, the drop in SI we observed in myocardium exposed to a stenotic coronary artery reflects a decline in myocardial oxygenation because of vasoconstriction caused by hyperoxia. Several recent studies have used OS-CMR to monitor changes of myocardial oxygenation after changing blood gas levels, especially O2 and CO2.3,10,11,30 Those studies showed that OS-CMR is a reliable tool to assess the impact of hyperoxia on myocardial oxygenation.31

Coronary artery stenosis in our animals was verified by an FFR of <0.75.32 Consistent with other studies, we used a PaO2 of >300 mmHg for hyperxia.3,27,30 compared with a physiological level of 100 mmHg. Our model allowed for a tightly controlled setting, which is difficult to achieve in patient studies. Confirming the observations of McNultry et al.4 we found a substantial decrease in blood flow in the LAD during hyperoxia.4 Adding further vasodilating (hypercapnia) and vasoconstricting (hypocapnia) stimuli we also wanted to investigate if the hyperoxic vasoconstriction could be further aggravated or attenuated. Although not significant, we found a relationship between the PaCO2 level and the decrease in LAD blood flow in both groups.

The decrease in myocardial oxygen extraction during hyperoxia somewhat contradicts the underlying

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<tr>
<th>Level</th>
<th>Control</th>
<th>Stenosis</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100/40</td>
<td>54±4%</td>
<td>48±3%</td>
<td>0.26</td>
</tr>
<tr>
<td>300/30</td>
<td>56±4%</td>
<td>41±5%</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>300/40</td>
<td>56±3%</td>
<td>42±4%</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>300/50</td>
<td>49±7%</td>
<td>41±6%</td>
<td>0.43</td>
</tr>
<tr>
<td>Cardiac output</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100/40</td>
<td>2813±294</td>
<td>2073±171</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>300/30</td>
<td>3246±303</td>
<td>2175±180</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>300/40</td>
<td>3217±308</td>
<td>2275±147</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>300/50</td>
<td>3111±406</td>
<td>2125±287</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Differences between control and stenosis animals in ejection fraction (EF) and cardiac output (CO). We find differences in EF and CO between control and stenosis animals during hyperoxia. Levels reported as PaO2 (mmHg)/PaCO2 (mmHg), mean±SEM.

*Difference statistically significant (P<0.05).

Figure 3. Peak circumferential strain during hyperoxia. Peak myocardial strain during hypoxia (300/30), normoxia (300/40), and hyperoxic hyperoxia (300/50) in healthy (Hea.) and animals with a significant left anterior descending coronary artery (LAD) stenosis (Sten.). In the animals with a significant coronary artery stenosis, peak myocardial strain was found to be reduced in the LAD region compared with baseline strain (P<0.05). There was no change in strain in the LAD territory of healthy animals or remote myocardium. However, hypocapnic hyperoxia resulted in a drop on global circumferential strain in the healthy animals. Levels expressed as PaO2 (mmHg)/PaCO2 (mmHg), mean±95% confidence intervals, *P<0.05.
pathophysiology: with reduced oxygen delivery because of coronary vasoconstriction a higher oxygen extraction is to be expected, especially in the already ischemic animals. However, this decrease in myocardial oxygen consumption is well in-line with literature.30-35 High oxygen tensions seem to decrease capillary density with a consequent reduction of oxygen diffusion and thus extraction. Increasing CO₂ levels seem to attenuate this effect.

Interestingly, looking at peak circumferential myocardial strain after inducing hyperoxia, we saw a reduction in myocardial strain in the LAD perfusion territory that was absent in the remote myocardium and in the LAD territory of the healthy animals, supporting the concept that the myocardial hyperoxia-aggravated ischemia was severe enough to result in a local myocardial dysfunction. The reduction in global myocardial strain during hyperoxic hypocapnia can be explained by the combination of 2 vasoconstrictive stimuli.

The fact that only the midapical slice showed significant differences in myocardial SI in OS-CMR images can be explained by the fact that the midventricular slice may have been placed too close to the occluder. The proximal slice may be perfused mainly by vessel proximal to the stenosis, whereas in the lower slice the stenosis has a full effect.

Our data are in line with findings of previous studies and extend the concept further by directly demonstrating an exacerbation of myocardial ischemia by hyperoxia. The results of this pilot study now warrants for larger clinical studies with follow-up to investigate the role of hyperoxia in myocardial ischemia and also the cause of in-hospital deaths after ROSC. We also expect our findings to provide further evidence supporting caution in the use of oxygen in anaesthesia, especially in known coronary artery disease. If confirmed, current guidelines on the use of oxygen in cardiac patients may have to be revised.

Limitations

This study is limited by the small sample size. Also anaesthesia itself is a confounding factor altering vital parameters, potentially inducing ischemia and also reducing tissue oxygen demand. In our study, the animals also had an acute stenosis, with a pathophysiology different from chronic coronary artery disease. In this study, only female pigs have been used. This may be a confounder as hyperoxia and its subsequent mechanisms could vary as a function of sex. Although no animal model can perfectly resemble human physiology, coronary anatomy, and collateral blood flow in swine is considered similar to humans.36

Conclusions

In the presence of severe coronary artery stenosis, hyperoxia induced by oxygen administration not only reduces coronary blood flow but also leads to a regional decrease in myocardial oxygenation and myocardial function. Thus, the administration of excess oxygen in patients with severe coronary artery stenosis may exacerbate ischemia. Further research is required and current clinical practice may have to be revisited.

Acknowledgments

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Disclosures

Dr Friedrich is board member, advisor, and shareholder of Circle Cardiovascular Imaging Inc., the manufacturer of the software used for CMR image evaluation. Dr Friedrich, Dr Guensch, and K. Fischer have a pending international patent for the use of breathing maneuvers for diagnostics purpose. The other authors report no conflicts.

References


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