As an aerobic organ in a living body, the beating heart relies almost exclusively on the oxidation of energy-providing substrates such as free fatty acids (60-90%) for its primary contractile function. Specifically, chemical energy is generally produced in aerobic metabolic pathways through oxidative phosphorylation of ADP to ATP. Myocytes utilize the chemical energy stored in ATP molecules and transform it into mechanical energy. Accordingly, cardiac cells have to consume large amounts of \( \text{O}_2 \) for the contraction process, which accounts for over 80% of oxygen cost. The remaining <20% is consumed by other physiological processes not directly associated with contraction, i.e., membrane depolarization and repolarization. For this reason, the heart can only develop a small oxygen debt. Oxygen supply and demand has to match to maintain normal myocardial contractility.

Myocardial ischemia exists when the supply of oxygen to the myocardial tissue is inadequate for the metabolic oxygen demand of myocardium. This is usually caused by upstream coronary artery stenosis that reduces blood supply (coronary artery disease or CAD). Clinically, myocardial hypoxemia results in arrhythmia, angina, and regional or global impairment of ventricular function (1). Severe and prolonged imbalance between oxygen supply and demand will eventually lead to myocardial infarction. In addition, ischemia may still present even though the coronary artery flow is maintained due to an imbalance between oxygen supply and demand secondary to the increased myocardial metabolic requirements. As with severe systemic hypertension, the whole heart becomes ischemic. Measuring and quantifying the balance of myocardial oxygenation would provide direct assessment of the status of myocardial oxidative metabolism and ischemic status.

In current clinical practice, X-ray angiography is considered the gold standard for diagnosis of coronary artery stenosis. However, measurement of coronary artery stenosis by angiography is not always a reliable indication of the functional consequence of stenosis in CAD patients. Any variations, e.g., irregular atherosclerotic plaque, variable collateral flow, preexisting ventricle remodeling, etc. will alter the effect of coronary artery stenosis. Currently, cardiac PET has been the major image modality for absolute quantification of regional myocardial perfusion and oxygen metabolism (2). Investigators have shown that PET permits accurate quantification of regional myocardial blood flow (MBF) (3-5) with \( ^{15}\text{O}\)-water, and of myocardial oxygen consumption rate (MVO\(_2\)) (6-9) with \( ^{11}\text{C}\)carbon-acetate. Perfusion-MVO\(_2\) (supply-demand) mismatches were found in CAD patients with significant single-vessel left anterior descending (LAD) stenosis (>70%) using \( ^{11}\text{C}\)-acetate PET, despite normal regional left ventricular contractile function at rest (10). Of note, quantitative measurements of MVO\(_2\) and oxygen extraction fraction (OEF) using \( ^{15}\text{O}\)labeled oxygen gas were also reported in animals and healthy volunteers (11), and evaluated in patients (12). However, low spatial resolution (not suitable for the detection of subendocardial perfusion defects), relatively long acquisition time, limited availability, relative high cost, and ionizing radiation discourage the widespread use of PET for these purposes.

MRI is a non-invasive imaging modality that provides excellent image spatial resolution and soft tissue contrast, does not require iotinated contrast media or ionizing radiation, and is widely available. Cardiac functional MRI demonstrated myocardial blood oxygenation qualitatively evaluated in animals and humans using the BOLD (Blood Oxygen Level Dependence) effect (13-19), which is the fundamental mechanism for detecting tissue and blood oxygenation in MRI (20-23). Thulborn et al. (24)
first recognized the BOLD effect: that the presence of paramagnetic deoxyhemoglobin in red blood cell affects blood T₂ relaxation rate in vitro. This observation was confirmed and validated by others (25-30). Early studies in the heart indicated myocardial relaxation time T₂ * (1/T₂ * = 1/T₂ + 1/T₂ ′ and T₂ ′ is related to the magnetic field inhomogeneity) changes with alterations in total tissue deoxyhemoglobin concentration. Since then, myocardial T₂ * or T₂-weighted imaging, which is usually acquired by gradient-echo (GE) sequences, has been explored by many investigators to assess the change in myocardial oxygenation in cardiac MRI (31-35).

Semi-quantitative assessment of myocardial oxygenation

In earlier work, T₂ * contrast was usually applied to assess the change in myocardial oxygenation following pharmacologically induced hyperemia (Table 1) (36,37). The typical sequence was a segmented multi-echo gradient echo with ECG triggering and black-blood dual-inversion-pulse preparation. Data acquisition occurred mid-diastole to minimize cardiac motion. Because of the T₁ effects from heart rate variation, e.g., from resting to vasodilation, absolute T₂ * value is preferred for assessing BOLD contrast. From literature published so far, the sensitivity and specificity to detect significant coronary artery stenosis are approximately 90% and 70%, respectively.

However, T₂ * contrast is sensitive to bulk susceptibility artifacts (19), field inhomogeneity, and magnetic field shimming status (28). Reproducibility of T₂ * measurement is poor for different regions of the myocardium on an intra- and inter-subject basis. In contrast, T₂ or T₂-weighted contrasts are more physiologically relevant. Compared to T₂ * contrast, sensitivity to oxygenation with T₂ contrast is reduced for all vessel sizes, but it is much less sensitive to changes in hematocrit, temperature, and field inhomogeneity. In the heart, capillaries contribute over 90% of the microvascular blood volume (44,45). The change in T₂ due to changes in deoxyhemoglobin content reaches its maximum in capillary-size vessels (46). Because T₂ contrast is most sensitive to the changes in susceptibility and diffusion in the capillary system, T₂ may be a useful candidate for imaging microvasculature and vasodilatory alternations in myocardium quantitatively. Foltz and et al. (47) have demonstrated a significant correlation between regional myocardial T₂ in the left anterior descending (LAD) coronary artery territory and oxygen content in the LAD coronary vein. Ghugre et al. (48) applied T₂ BOLD contrast to image infarction and remote regions using an acute myocardial infarction porcine model. The changes of myocardial T₂ in both regions were observed throughout the infarction healing, which may indicate the status of left ventricle remodeling. In comparison with the T₂ * method, T₂ contrast clearly benefits from much higher image quality with acceptable BOLD sensitivity (approximately 10% at 1.5 T, and 15% at 3 T). Another interesting method is to use phase resolved BOLD MRI (49) that can readily assess changes in myocardial oxygenation and blood volume in different cardiac cycles. Myocardial ischemia can be detected even at rest with this approach (50).

Table 1 Summary of major references for myocardial oxygenation assessment in patients with coronary artery disease

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Authors</th>
<th>Sequences</th>
<th>References</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₂ *</td>
<td>Niemi et al. (15)</td>
<td>GE, TE =45 ms</td>
<td></td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Li D et al. (16)</td>
<td>GE, TE =16, 25 ms</td>
<td></td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Wacker et al. (19)</td>
<td>GE, TE =6-54 ms</td>
<td></td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Beache et al. (35)</td>
<td>GE, TE =2-26 ms</td>
<td>X-ray &amp; SPECT</td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Friedrich et al. (36)</td>
<td>GE, TE =17.4 ms</td>
<td>¹⁸FDG-PET</td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Egred et al. (37)</td>
<td>GE, TE =28 ms</td>
<td>X-ray</td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Manka et al. (38)</td>
<td>GE, TE =2.7-11.2 ms</td>
<td>X-ray</td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td>T₂</td>
<td>Bernhardt et al. (39)</td>
<td>T₂-prep SSFP</td>
<td>CMR perfusion</td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Karamitsos et al. (40)</td>
<td>T₂-prep SSFP</td>
<td></td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Jahne et al. (41)</td>
<td>T₂-prep GRE</td>
<td>X-ray</td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Walcher et al. (42)</td>
<td>T₂-prep SSFP</td>
<td>Fractional flow reserve</td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
<tr>
<td></td>
<td>Arnold et al. (43)</td>
<td>T₂-prep SSFP</td>
<td>X-ray</td>
<td>78-88%</td>
<td>46-68%</td>
</tr>
</tbody>
</table>
Recent clinical applications of $T_2$-based method has primarily used $T_2$-weighted imaging that was first proposed by Li et al. (51) and then validated in a canine model (52). Advanced development in cardiac TrueFISP (True Fast Imaging with Steady State precession) imaging allows high quality of $T_2$-weighted TrueFISP to assess BOLD contrast in a clinical setting (39,40,43). The typical sequence is a 2-dimensional $T_2$-prepared segmented TrueFISP acquisition with a $T_2$ preparation time of 40 ms. For the minimization of cardiac and respiratory motion, data is acquired mid-diastole with breath-hold by the subject. BOLD contrast has to be determined before and after adenosine administration from the change in signal intensity. Figure 1 shows the detection of coronary artery stenosis using a BOLD index derived from $T_2$-weighted images, demonstrating the sensitivity of this technique. Several manuscripts have been recently published using this technique. Relatively high sensitivity and specificity can be achieved >90% in the detection of coronary artery diseases in comparison with PET perfusion (53), X-ray angiography (38,41), and fractional flow reserve (42). Interestingly, by comparison with PET or MRI perfusion measurements, regions of deoxygenation sometimes mismatch with the regions of hypoperfusion (43,53), and tissue oxygenation correlates poorly with quantitative coronary angiography (43). The underlying mechanism remains unclear, but it postulated that myocardial autoregulation, ATP usage, and myocardial blood volume may play certain roles for this process.

Quantitative assessment of myocardial oxygenation

Quantitative myocardial oximetry was developed previously to establish the relationship between blood $T_2$ and oxygen saturation (30). The method was further evaluated in vivo for coronary sinus oxygenation in adults (54) and in infants (55). Using the same approach, measurements of global left ventricular MVO$_2$ and whole body oxygen consumption (VO$_2$) were reported by Yang et al. (56). Both data are very comparable with reported PET and other invasive methods (MVO$_2$: 11±3 vs. 10±3 mL/min per 100 g LV mass; VO$_2$: 3.8±0.8 vs. 3.5 mL/min/kg body weight). Furthermore, the reproducibility of their measurements is relatively high (coefficient of repeatability of 1.0 mL/min per 100 g LV mass).

Another approach to assess myocardial oxygenation is to measure myocardial oxygen response during a vasodilation or stress (hyperemia). A MRI method was developed to derive hyperemic myocardial OEF by taking advantage of the BOLD effect in myocardial $T_2$ (57). When myocardial flow increases during hyperemia, normal myocardial $T_2$ will increase secondary to reduced deoxyhemoglobin concentration. With excessive oxygen supply, myocardial OEF will reduce in normal myocardial tissue, but will remain the same or even increase in ischemic tissue. A two-compartment diffusion model was created to calculate hyperemic OEF, based on known or assumed resting myocardial OEF. The data acquisition is performed
using a 2D multi-contrast segmented turbo spin-echo sequence to generate T$_2$-weighted images that are used to calculate pixel-by-pixel T$_2$ maps.

In a validation study using a coronary artery disease model in canines, PET imaging was used as the reference method to measure myocardial transmural OEF and MVO$_2$ (58). Overall there were no significant errors and the MRI OEF results were closely correlated with the reference PET measurements. MRI measurement of MVO$_2$ slightly overestimated PET results, but with a very strong linear correlation (slope =0.83; intercept =1.41; r=0.86, P<0.001). These technical developments demonstrated promising alternatives to nuclear techniques because they could be used for serial assessments of myocardial oxygenation in settings of regional or global myocardial ischemia without worrying about excessive radiation.

In the latest development, another T$_2$ sequence, bright-blood T$_2$-prepared-gradient-echo or T$_2$-prepared TrueFISP sequence, was modified to calculate myocardial T$_2$ maps using 4-5 T$_2$-weighted images within one breath-hold (59). Resting OEF in the coronary sinus, representing global myocardial OEF, can also be calculated through a blood-oxygen model. The main limitations of the sequence are relatively low spatial resolution and limited precision. The sequence is also sensitive to both respiratory and cardiac motion, particularly at higher heart rates. In addition, calculation of myocardial OEF remains complicated. Further technical improvement is needed to reduce motion artifacts, acquire more T$_2$-weighted images to increase the precision of myocardial T$_2$ measurements, and to streamline model calculation for clinical practices.

In summary, MRI based myocardial oxygenation imaging is an attractive non-invasive approach to assess myocardial oxygen supply and demand. Although the T$_2$* method demonstrated great sensitivity detecting changes in myocardial oxygen content, T$_2$-based high-contrast SSFP imaging has earned an important role in a clinical setting, owning to its good sensitivity and high image quality. Quantitative measures using either absolute myocardial T$_2$ or related modeling for OEF calculation could allow consecutive monitoring of dose response of medical therapy. However, more technical innovations (multi-slice, higher spatial resolution for endocardial assessment, better sensitivity, etc) and systematic evaluation are warranted before exploring for full clinical applications.

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