The diagnosis of silent myocardial ischemia. Motion-Frozen (or morphing) myocardial perfusion imaging

Cheng Chang[1*] MD, Bo Ye[2*] MD,Wenhui Xie[1] MD, Daoliang Zhang[3] MD,Bei Lei[1] MD, Xiaodan Ye[4] MD

1. Department of Nuclear Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China
2. Department of Thoracic Surgery,Shanghai Chest Hospital, Shanghai Jiao TongUniversity, Shanghai, China
3. Department of Cardiology, Shanghai ChestHospital, Shanghai Jiao Tong University,Shanghai, China
4. Department of Radiology, Shanghai ChestHospital, Shanghai Jiao Tong University, Shanghai, China

**Cheng Chang and Bo Ye contributed equally to this article.*

Corresponding author: Wenhui Xie MD, E-mail: xiewhwh@163.com, 241 West Huaihai Road, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China. Tel: 0086-021-2220000-1701

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Abstract
Silent myocardial ischemia is typically defined as objective evidence of myocardial ischemia in patients without subjective ischemia symptoms. Currently, coronary artery angiography is the gold standard for diagnosis of asymptomatic coronary artery disease (CAD). Computed tomography coronary angiography (CTCA) can visually demonstrate the morphology, trend and extent of coronary stenosis and is commonly used in clinical screening of CAD. Myocardial perfusion imaging can be used not only to identify whether anatomical stenosis causes myocardial dysfunction, but to also assess the risk stratification and prognosis of myocardial disease (MD). Myocardial perfusion imaging using morphing combined with CTCA can simultaneously show the relationship between CAD and myocardial ischemia from an anatomical and functional aspect. This allows earlier diagnosis of asymptomatic CAD myocardial ischemia, accurate identification of the culprit vessels, and could prevent unnecessary interventional therapy. The 1-day dobutamine stress/resting met-hod is also one of the methods used. The combination of CTCA and the morphing technique can provide anatomical and functional information on coronary arteries at the same time, significantly improving the diagnostic sensitivity, specificity, and accuracy of MD.

Introduction

Silent myocardial ischemia (SMI) is the most common manifestation of coronary artery disease (CAD). Silent myocardial ischemia is typically defined as objective evidence of myocardial ischemia in patients without subjective ischemia symptoms. Silent myocardial ischemia may be detected in patients who have no symptoms during an exercise or pharmaceutical stress test, but who do have transient ST-segment changes, perfusion defects, or reversible regional wall motion abnormalities [1]. Therefore, SMI is also known as painless myocardial ischemia or occult myocardial ischemia [2, 3]. Occult onset of SMI exists in various types of CAD, which leads to the occurrence of various types of cardiac events. Silent myocardial ischemia that can easily be ignored by patients can further increase the incidence of myocardial infarction and sudden death of CAD [1].

Coronary artery angiography

Currently, coronary artery angiography (CAG) is the gold standard for diagnosis of asymptomatic CAD. Coronary artery angiography can directly identify whether the coronary artery and its branches are striated, as well as the severity of striation. However, CAG is an invasive approach with certain risks, and it cannot be used as a screening method. Coronary artery angiography is also the gold standard for diagnosis of CAD morphology, and shows anatomical stenosis of coronary blood vessels at the millimeter level or above. However, CAG does not reflect myocardial perfusion at the terminal coronary circulation. In patients with SMI, false negative findings may occur. Misdiagnosis can occur because of coronary artery spasms caused by reduced local blood flow reserve when the extent of stenosis is between 40% and 70%. When the coronary artery enters the diffuse and extensive phase, the reference vascular segment in CAG may also be striated, and CAG cannot accurately reflect the degree of coronary artery stenosis. Furthermore, when myocardial ischemia is caused by thrombosis in the coronary artery, the thrombosis may have dissolved prior to CAG examination, and may lead to normal images displayed in CAG [4].

Computed tomography coronary angiography

Computed tomography coronary angiography (CTCA) can visually demonstrate the morphology, trendand extent of coronary

stenosis and is commonly used in clinical screening of CAD [5, 6]. The CTCA image data provide by the 64-slice spiral computed tomography (Brilliance 64; Philips Medical System, Eindhoven, Netherlands) transmitted to a computer workstation (Mxview, Philips Medical Systems) and collected using intelligent software (care bolus) technology for tracked scanning. The original data are reconstructed using the maximum density method and surface reconstruction method [7, 8]. The high negative predictive value of CTCA in the diagnosis of SMI has important clinical value. However, CTCA also has limitations because the quality of CTCA images is affected by heart rate, respiration and noise resulting in false negative findings [9]. Furthermore, even though coronary artery calcification can provide anatomical information on coronary atherosclerosis, calcification is also an important factor causing attenuation of X-rays and high-density artifacts [10, 11]. Additionally, severe calcification can decrease the accuracy of vascular evaluation. The biggest limitation of CTCA is that it may not reflect the function of myocardial cells in the region supplied by the coronary artery. Coronary artery spasms and collateral circulation formation posterior to stenosis can lead to inconsistency regarding anatomical striation of the coronary artery and myocardial perfusion at the terminal coronary circulation. Therefore, coronary artery stenosis identified by CTCA does not necessarily mean that there will be abnormal myocardial perfusion. The extent of luminal stenosis is one of many factors affecting myocardial perfusion, but may not be the decisive factor [12].

Computed tomography coronary angiography has a high accuracy for detecting Coronary artery calcium score, degree and extent of SMI compared with invasive coronary angiography [6, 13].

Myocardial perfusion imaging and Motion-Frozen (morphing) method

Myocardial perfusion imaging can be used not only to identify whether anatomical stenosis causes myocardial dysfunction, but to also assess the risk stratification and prognosis of SMI. There are many factors that can affect myocardial perfusion imaging. These factors include blurring effects caused by heart beats, the attenuation effect of the female breast decreasing radioactivity of the front wall, a diaphragmatic attenuation effect in males and decreasing radioactivity of the inferior and posterior wall [14, 15]. The morphing technique tracks the left ventricle through all cardiac phases. Thereafter, this technique shifts the counts from most phases of the cardiac cycle (excluding the systolic frames) to the end-diastolic position by means of nonlinear image warping [16]. The acquisition data were used by GE Xeleris workstation (GE Medical Systems) of GE Discovery D670 Single Photon Emission Tomography (SPET, GE Medical Systems, USA) for automatic processing. The imaging data from 63% of the cardiac cycle are used, excluding three phases for eight frames close to the end-systolic phase. Nonlinear image warping of selected cardiac phases to the spatial position of the end-diastolic phase is subsequently performed on the basis of the three-dimensional displacement vectors [16]. Myocardial perfusion imaging using morphing of the left ventricle is reconstructed with a matrix of 64×64. To determine whether the subject examined moved during the examination, a film display and sonogram is used. Motion correction software with reacquisition is used to correct the image when necessary.In a prototype study of ours in 56 patients we found that this technique is better than not morphing because morphing technology can improve the quality of myocardial perfusion images [17]. Morphing technology may decrease interference of the above factors to a certain degree [17, 18]. Morphing technology uses images of the heart at each phase of the cardiac cycle during gated myocardial perfusion,to achieve cardiac morphing of images of the short axis.Myocardial perfusion imaging using morphing is the image of non-gated myocardial perfusion obtained using morphing [19]. Therefore, the morphing technique can display non-gated MPI images of the left ventricle with high resolution via morphing of gated MPI images at different phases [20]. Myocardial perfusion imaging using morphing technology can significantly improve the signal-to-noise ratio of left ventricular wall images [17, 21]. Neither CTCA nor CAG can accurately diagnose myocardial ischemia caused by coronary microvascular disease because of limited anatomical resolution. Myocardial ischemia caused by coronary microvascular disease can easily be diagnosed by MPI [22]. The so-called false positive findings in MPI using morphing may not necessarily be real false positive, and should be carefully determined by clinical judgment after elimination of all other possibilities. Myocardial perfusion imaging using morphing has limitations: Determines blood perfusion abnormalities based on the relative distribution of a myocardial imaging agent. This agent mainly reflects the region, range, and extent of the most severe lesions of one or two culprit vessels in patients with three-branch SMI. Therefore, the severity of coronary lesions can be underestimated and likely may cause missed diagnosis of balanced three-vessel stenosis [4, 23, 24].

Myocardial perfusion imaging using morphing combined with CTCA can simultaneously show the relationship between CAD and myocardial ischemia from an anatomical and functional aspect. This allows earlier diagnosis of asymptomatic CAD myocardial ischemia, accurate identification of the culprit vessels, and could prevent unnecessary interventional therapy [25, 26]. Hacker et al. (2007) [27] combined CTCA and MPI to explore function-related coronary artery lesions. They showed that the combination of CTCA and MPI could accurately determine the morphology and function of the corresponding coronary artery. Gaemperli et al. (2009) [28] integrated the images of CTCA and MPI to gain more morphological information on coronary artery lesions. This process improved the diagnostic accuracy and avoided unnecessary interventional therapy in more than one-third of the patients. According to our studies, the sensitivity, specificity, and diagnostic accuracy of CTCA combined with MPI using morphing were 93%, 81%, and 88%, respectively, which were significantly higher than those of CTCA (74%, 72%, 73%, respectively) and of MPI using morphing (81%, 74%, and 78%, respectively). The Kappa value for the diagno-sis of SMI using MPI with morphing combined with CTCA was 0.75.

Technetium-99m-hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) data analysis

The 1-day dobutamine stress/resting method is one of the methods used. A UT400B type ECG defibrillation instrument (China Shenzhen Goldway Co., Ltd.) is connected to the limb of supine patients to record resting heart rate, blood pressure, and ECG prior to the examination. Dobutamine (purchased from Shanghai First Biochemical Pharmaceutical Co. Ltd., 20 mg [2mL]) is injected intravenously at a rate of 5g/kg/min. This dose is gradually increased by 5g/kg/min to 40g/kg/min with continuous infusion of 3min at each level. Heart rate, blood pressure, and ECG of the patients at each level are recorded during the intravenous infusion. The examination is terminated when the heart rate reaches 85% of the expected highest heart rate (or ⩾130bpm), including serious arrhythmia, systolic blood pressure ⩾210mmHg (1mmHg= 0.133kpa), blood pressure decreased by 22.5mmHg, or the ST segment decreased by ⩾2mm. An intravenous injection of ^{99m}Tc-MIBI (radiochemical purity >95%, from Shanghai Xinke and Shanghai Kexin Pharmaceutical Co., Ltd.) of 296-370MBq is administered at the peak of dobutamine stress or on the appearance of the termination index, with an oral fatty meal (250mL milk) provided to the patients 30min later. This is followed by image acquisition at 1.0-1.5h after the injection. After another 3-4h, ^{99m}Tc-MIBI of 925-1110MBq is administered intravenously. This is followed by oral administration of a fatty meal (250mL milk) 30min later and image acquisition at 1.0-1.5h after the injection. Acquisition is performed using a GE Discovery D670 SPET (GE Medical Systems, USA) with a double probe in the "L" mode. A low-energy, high-resolution collimator is configured to collect eight phases at each cycle of the RR interval, for 60sec at each projection. A total of 30 projections, and the acquisition matrix 64×64 is used. The acquisition data by GE Xeleris workstation (GE Medical Systems) for processing are used. The Ordered Subsets Expectation Maximization method is used to reconstruct MPI images of the left ventricle at each phase.

The efficiency of this technique to diagnose SMI is a new method improving diagnostic efficiency

The results of MPI using morphing are based on the blood supply distribution of the three major coronary arteries. The blood supply area of the left anterior descending artery includes the anterior wall, the base of the anterior wall, the anterior septum and the apex of the heart. The blood supply area of the left circumflex artery includes the anterior lateral wall and the posterior lateral wall of the heart. The blood supply area of the right coronary artery includes the posterior septum, the inferior wall, and the posterior wall. The images are evaluated according to conventional diagnostic criteria (the presence of segmental radionuclide defects in different sections for two layers or more are considered positive). Defects are divided into reversible defects, irreversible defects, and mixed defects. Coronary artery stenosis <70% without myocardial ischemia/infarction is considered normal. Coronary artery stenosis ⩾70% and/or myocardial ischemia/infarction is considered abnormal [8, 29].

The combination of CTCA and the morphing technique can provide anatomical and functional information on coronary arteries at the same time, significantly improving the diagnostic sensitivity, specificity, and accuracy of SMI [30-32].

In conclusion, as noninvasive diagnostic imaging methods of SMI, MPI using morphing and CTCA have satisfactory diagnostic efficiency. Dobutamine stress/resting MPI with morphing technique can provide accurate information on myocardial perfusion from the functional aspect. Computed tomography coronary angiography can not only determine the extent of coronary artery stenosis, but also shows the extent, scope, and nature of atherosclerosis of the vessel walls. The combination of CTCA and the morphing technique can provide anatomical and functional information on coronary arteries at the same time, significantly improving the diagnostic sensitivity, specificity, and accuracy of SMI.

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