PET/MR co-imaging in cardiovascular diseases: Current clinical applications and future development

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Abstract

Objective: This paper reviews the current status and future development of positron emission tomography/magnetic resonance (PET/MR) co-imaging technology in the field of cardiovascular diseases. **Materials and Methods:** By combining PET and MRI, PET/MR co-imaging provides comprehensive assessment advantages by simultaneously offering functional and anatomical information. **Results:** Firstly, the basic principles of PET/MR are introduced, and the current state is discussed. Subsequently, a detailed discussion on the application of PET/MR in the diagnosis of cardiovascular diseases, including early detection and comprehensive assessment of conditions like coronary artery disease and myocarditis, is presented. Finally, the challenges and future prospects in PET/MR applications are outlined. **Conclusions:** Despite facing several technical challenges, PET/MR co-imaging technology is expected to play a crucial role in the early diagnosis, treatment, and research of cardiovascular diseases, paving the way for new directions and possibilities in future medical imaging research.

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Introduction

Cardiovascular diseases have consistently been a focal point of concern in healthcare systems and global health. Their high incidence and life-threatening nature make them a significant challenge in medical research and clinical practice [1, 2]. With the continuous advancement of science and technology, the development of medical imaging has provided a powerful tool for in-depth studies of cardiovascular diseases. In this context, the emergence of positron emission tomography/magnetic resonance (PET/MR) co-imaging technology offers a novel approach for the seamless fusion of anatomical structure and biological functional information, representing one of the most advanced techniques in the fields of functional and molecular imaging. Positron emission tomography and MRI have each achieved significant accomplishments in medical imaging with their unique advantages. Positron emission tomography, with its high sensitivity to molecular metabolic activity, serves as a powerful tool for probing biological processes. On the other hand, MRI, with its outstanding anatomical resolution and tissue contrast, is the preferred method for acquiring detailed anatomical structures. The integration of these two modalities in PET/MR examinations maximizes the complementarity of anatomical and functional information. Therefore, current clinical applications of PET/MR are primarily focused on oncology, cardiovascular diseases, and neuroscience.

This paper aims to comprehensively review the latest research developments of PET/MR co-imaging technology in cardiovascular diseases, exploring its potential applications in diagnosis, treatment, and research within the cardiovascular domain. The goal is to provide a comprehensive reference for researchers in the field of medical imaging, driving advancements in the domain and offering new perspectives for future clinical practices.

Current status

Experts and scholars propose that PET/MR is considered the gold standard diagnostic tool for tumors, neuro-psychiatric diseases, and cardiovascular diseases. The combination of PET molecular imaging with multi-specific tracers and MR's multi-sequence, multi-parameter anatomical and functional imaging creates a synergistic effect, making PET/MR an irreplaceable tool in the diagnosis and treatment of diseases [3, 4]. In the realm of oncology, PET/MR is applicable for early diagnosis, differential diagnosis, clinical staging, and efficacy evaluation in various cancers such as prostate cancer, liver cancer, endometrial cancer, brain tumors, and intraspinal tumors. Compared to PET/CT, PET/MR complements the diagnosis, staging, and efficacy assessment of these tumors. In the early screening of elevated tumor markers and high-risk populations, PET/MR exhibits higher accuracy. Additionally, in the diagnosis of challenging conditions like unexplained fever, PET/MR holds significant clinical value. Positron emission tomography/MR imaging enables precise localization and quantitative analysis of brain lesions, revealing metabolic, morphological, and functional abnormalities at the molecular and macroscopic levels. This enhances the accuracy of diagnosis and treatment evaluation for neuro-psychiatric diseases, covering Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, brain and spinal cord tumors, among others. In the field of cardiovascular diseases, PET/MR can evaluate cardiovascular anatomy, function, myocardial perfusion, and myocardial vitality. It is employed for risk stratification, prognosis assessment, and guiding treatment. Commonly used for assessing coronary artery disease, myocardial ischemia, left ventricular function, surviving myocardium post-infarction, scar extent, and imaging arterial atherosclerotic plaques, PET/MR holds significant clinical value in the diagnosis of myocardial diseases and arterial plaques [5, 6]. Importantly, the continuous development of specific radiolabeled tracers allows imaging of an increasing number of disease-specific molecular targets. This includes over 20 specific imaging agents such as gallium-68-prostate specific membrane antigen (^{68}Ga-PSMA), ^{68}Ga-fibroblast activation protein inhibitor (FAPI), fluorine-18 (^{18}F)-P3BZA, ^{68}Ga-octreotide, ^{68}Ga-Pentaxfor, ^{18}F-AV45, ^{18}F-l-3,4-dihydroxyphenylalanine (DOPA) etc., which can be utilized for early diagnosis, lesion localization, qualitative and quantitative diagnosis, and treatment guidance in diseases like prostate cancer, liver cancer, brain and spinal cord tumors, malignant melanoma, neuroendocrine tumors, primary aldosteronism, Alzheimer's disease, Parkinson's disease, and myocardial diseases.

Currently, Siemens, Philips, and GE companies have launched related PET/MR products, successfully extending them to clinical applications. The fusion modes of PET/MR co-imaging mainly fall into three categories. Firstly, PET and MRI scanners are connected in series: two independent systems are connected, sharing a scanning bed for simultaneous independent use. This design is similar to PET/CT, where both systems can be used independently, but it poses some challenges such as large space occupation, inability to acquire data simultaneously, long total scanning time for two full-body scans, and the possibility of mismatched images due to patient motion and physiological activities during scanning. Secondly, the insertion of PET scanners: a movable PET tomography scan is inserted into the MRI aperture. The advantage of this method is achieving PET and MRI data acquisition simultaneously, ensuring their perfect fusion while shortening the total acquisition time. However, inserting PET may reduce the size of the scanning aperture, limiting its application. The only example currently is the PET insert for 3T MRI based on APD, successfully used for imaging the human brain, head, and upper neck. Lastly, the fully integrated PET/MR: integrating the PET detector ring entirely onto the MRI scanning framework for whole-body image data acquisition. This is the most technically challenging method, with higher costs and technical requirements for operators. Some research teams have attempted to place PET detectors between the two super conducting magnets of an MRI or designed a PET/MR integrated machine that can only operate at low magnetic fields. However, due to technical limitations, this approach has not yet become a reality.

Technical challenges

Based on previous literature, the integration of PET and MRI faces several technical challenges, including equipment compatibility, attenuation correction (AC), and motion correction (MC) for PET, as well as the standardization of the scanning process.

The first challenge is related to hardware composition: Compatibility issues primarily involve the stability of PET hardware in electromagnetic environments and ensuring that PET signal acquisition does not interfere with MRI. Currently, PET/MR utilizes avalanche photodiode or silicon photomultiplier instead of traditional PET photomultiplier converters. This involves embedding PET detection components between the MRI radiofrequency and gradient systems using electromagnetic shielding techniques and low-attenuation materials. The second challenge is attenuation correction: PET/MR's AC involves both hardware structure and human tissue aspects. While low-attenuation materials are used in hardware structure, the system stores attenuation coefficient maps. However, challenges arise with the tissue segmentation method based on Dixon MRI sequences, which faces difficulties in obtaining attenuation coefficient maps around bones [7, 8]. Additionally, this method categorizes bones and calcifications as soft tissue, potentially leading to underestimation of attenuation values for the heart tissue behind the sternum [9, 10]. Although ultra-short echo time sequences can provide attenuation correction for bones as a separate category, their small field of view and time-consuming nature currently limit their application in clinical cardiac PET/MR imaging. Moreover, the presence of metal implants and MRI contrast-enhanced imaging may also affect AC and requires further research.

The next challenge is motion correction: Motion correction is a major challenge for cardiac PET, mainly arising from respiratory and cardiac motion. Traditionally, motion gating methods use only a small amount of collected data (end-expiratory data for respiratory gating and end-diastolic data for ECG gating) for image reconstruction, resulting in low image signal-to-noise ratio. To enhance image quality and reduce examination time, motion correction can utilize all collected data for image reconstruction. Positron emission tomography/MR's motion correction is based on MRI methods to correct PET data, often using real-time three-dimensional MRI or tagging techniques to obtain patient motion information. Some research teams employ dual-gated MRI non-rigid registration techniques and have developed new image acquisition, post-processing, and reconstruction methods. Other research teams propose new methods based on MRI to correct PET quantitative measurement deviations. This involves converting the average density map of each basic motion region obtained from MRI into the PET space, constructing a system of linear equations and modeling, and solving for the true activity values. This method demonstrates higher accuracy and reliability compared to other simpler methods. Although MRI-based motion correction improves the reliability of results in low-dose or high-noise PET data, further research is still needed for routine clinical applications.

There are also challenges related to standardize scanning: PET/MR cardiovascular imaging involves challenges in patient training, positioning, and the selection of scanning sequences. Patient training includes respiratory and emergency training, and during positioning, metal objects need to be removed. The choice of scanning sequences and timing depends on factors such as the type of heart disease and the registration of attenuation coefficient maps with PET data, requiring further optimization and research.

Clinical applications

Coronary artery disease

Abundant clinical research data indicate that nuclear myocardial imaging plays a crucial role in diagnosing coronary artery disease, performing risk stratification, detecting viable myocardium, making treatment decisions, assessing efficacy, and conducting prognostic evaluations. Among these applications, nuclear myocardial perfusion imaging is considered a non-invasive method that provides accurate and well-evidenced support for diagnosing myocardial ischemia in patients with coronary artery disease. Previous studies have shown that the sensitivity and specificity of PET imaging in detecting coronary artery disease are 92% and 85%, respectively, while cardiac magnetic resonance (CMR) is 87% and 91%, respectively. Positron emission tomography is currently recognized as the "gold standard" for non-invasive detection of coronary flow reserve (CFR), while CMR, due to its high spatial resolution, can detect small sub-endocardial ischemic areas and diffuse myocardial fibrosis, providing important value in the diagnosis of myocardial ischemia and guiding the selection of treatment plans [13, 14]. Therefore, it can be considered that PET/MR joint diagnosis has potential advantages in the detection of coronary artery disease, such as evaluating wall motion abnormalities, detecting myocardium with localized and segmental reduction in motion, thickening myocardium, and scar tissue. Positron emission tomography/MR joint imaging, through a one-stop scan, can provide more comprehensive imaging diagnostic information on cardiac anatomy, blood flow perfusion, heart function, vessels, and tissue characteristics in the clinical setting. Under equivalent hemodynamic conditions, it excludes differences in physiological conditions at different measurement times, mutually confirming and supplementing each other. However, the clinical value of this information still requires large-sample clinical comparative studies, and currently, there is limited research in this area.

Cardiac nodules

Nodular disease is a multisystem granulomatous disorder, with autopsy results indicating that approximately 1/4 of nodular disease patients have cardiac involvement. The pathological basis of cardiac nodular disease involves granulomatous inflammatory reactions, followed by myocardial necrosis and fibrosis. Pathological biopsy (biopsy) is considered the "gold standard" for diagnosing nodular disease, and the American Heart Rhythm Society recommends performing a biopsy under the guidance of electrophysiology or imaging (PET/CT or CMR) to effectively increase the biopsy's positive rate. Previous studies have found that CMR LGE can assess myocardial scars, presenting as multifocal patchy enhancements, commonly seen in the basal regions (especially the interventricular septum and lateral wall); ^{18}F-FDG PET imaging can differentiate between the active and healing phases of inflammatory reactions in cardiac nodular disease, and whole-body imaging can simultaneously evaluate extra-cardiac nodular disease involvement. Positron emission tomography/MR, through CMR to identify fibrosis and ^{18}F-FDG to assess inflammatory reactions and accurately evaluate cardiac function, has important value in the diagnosis, activity assessment, risk stratification, prognosis, and efficacy monitoring of cardiac nodular disease.

Myocarditis

In recent years, PET and MRI have been widely used in the diagnosis and monitoring of inflammatory diseases, covering various diseases, including those affecting the heart. In reported cases of myocarditis using PET/MR, focal subepicardial LGE coincides with the suppression of normal myocardial glucose metabolism, accompanied by myocardial edema and congestion. Although MRI is sufficient for diagnosing myocarditis, PET can be used to assess the inflammatory activity of the heart and monitor treatment effects. In clinical guidelines for cardiac nodular disease, both PET and MRI are recommended for the diagnosis and evaluation of the disease. Late gadolinium enhancement imaging can display myocardial fibrosis in nodular disease, high ^{18}F-FDG PET uptake with normal perfusion suggests inflammatory activity, while reduced ^{18}F-FDG uptake and perfusion indicate inflammatory progression. Additionally, no ^{18}F-FDG uptake with or without low perfusion suggests the inflammatory end stage. Past studies also suggest the feasibility of PET/MR in the diagnosis and treatment monitoring of cardiac nodular disease [15, 16]. Therefore, PET/MR can not only diagnose cardiac involvement in nodular disease but also stage it, providing guidance for treatment.

Cardiac tumors

The clinical treatment approach for cardiac tumors depends on the tumor's malignancy and its location in the heart. Both standalone MR and PET have demonstrated high accuracy in the malignant diagnosis of cardiac tumors. Positron emission tomography/MR hybrid imaging can provide both anatomical and metabolic information for cardiac space-occupying lesions simultaneously, aiding in the diagnosis of tumor malignancy and assisting in surgical treatment planning and prognosis assessment. It can be speculated that

PET/MR will play an important role in preoperative planning for the infiltration range of some complex cardiac tumors or in distinguishing tumor recurrence from scar tissue after tumor surgery/radiotherapy. Scholars abroad have reported PET/MR imaging results for patients with cardiac space-occupying lesions, finding a sensitivity and specificity of up to 100%, demonstrating the added value of PET/MR in the diagnosis of cardiac tumors.

Other cardiovascular diseases

This includes various diseases such as atherosclerotic plaques and vascular lesions, myocardial amyloidosis, etc. Scholars in China conducted research on patients suspected of coronary artery disease, among which 13 out of 15 patients confirmed by biopsy showed positive PET results. In non-coronary artery disease patients, the UC-PIB PET scan results were all negative. There was a statistically significant difference in the uptake of HC-PIB in the myocardium between the non-chemotherapy group and the chemotherapy group ($P<0.05$). Therefore, PET/MR can not only diagnose and stage coronary artery disease but also evaluate treatment efficacy, especially suitable for patients who cannot undergo MRI LGE imaging, particularly those with impaired renal function. Other research results indicate a good correlation between lesions with a coronary artery high signal-to-normal myocardium signal ratio greater than 1.4 on the full-heart coronary atherosclerotic plaque qualitative technique (CATCH) sequence black blood map in CMR and vulnerable plaque scores detected by coronary optical imaging. Therefore, PET/MR imaging of atherosclerotic plaques at different targets has significant clinical application potential. Numerous studies on this topic exist in the literature, and we won't go into detail here [17, 18].

Discussion

Future prospects

As of October 2019, the National Health Commission has issued licenses for 28 PET/MR Class A large medical devices, marking a new development opportunity for PET/MR in China. However, the relatively high cost and technical complexity of PET/MR highlight the importance of professional training for PET/MR medical technicians in both PET and MRI-related knowledge. For example, in PET/MR examinations, there are absolute contraindications, such as pacemakers or implantable cardioverter-defibrillators, and mechanical heart valves. While coronary stents are mostly non-ferromagnetic or weakly ferromagnetic and are safe for CMR examinations, consultation or verification of the substance's safety for MR examinations is needed when dealing with other metal implants. Positron emission tomography/MR hybrid imaging integrates two powerful imaging modalities, providing significant advantages in clinical applications, but there are also limitations. These limitations include a smaller aperture, unsuitability for obese patients, higher costs, and issues like the absence of an MR-compatible ^{82}Rb generator and slower examination speed. In recent years, some small-sample research results have preliminarily demonstrated the potential application of PET/MR in ischemic heart disease, but its advantages in simultaneously collecting information have not been fully realized [19, 20]. Therefore, it is necessary to further improve technologies, including MR-based attenuation correction methods and motion correction methods. Despite some challenges in the current early stages of PET/MR technology research, the future development of imaging is no longer a revolution in a single technology but an integration of various technologies. As a multimodal imaging fusion technology, PET/MR integrates anatomical information, functional, and molecular-level information of biological tissues. Simultaneously, its safety and low radiation advantages endow it with significant medical and economic value. We believe that with the further development and improvement of PET/MR technology, its advantages in scientific research and clinical applications will greatly influence the direction of the entire medical imaging and medical science development. Additionally, radiotracers are considered the "soul" of nuclear medicine imaging. Currently, there is a wide variety of PET imaging agents for cardiovascular disease diagnosis, and many new drugs are under development. However, acquiring specific and targeted precursors or molecular probes has become a research challenge and hotspot in PET/MR imaging, affecting its clinical application value significantly. With the rapid development of nuclear fast labeling technology, molecular biology, nuclear chemistry, and molecular pharmacology, progress has been made in the development of PET/MR imaging agents. It is foreseeable that PET/MR has broad prospects for clinical applications, but it also faces significant scientific challenges. Looking to the future, PET/MR is emerging with advancements in science and technology and the needs of clinical and research. It has a broad application prospect in the diagnosis and auxiliary treatment of cardiovascular diseases. Future research can focus on optimizing MR sequences, shortening acquisition times, avoiding unnecessary duplicate information, and exploring PET quantitative methods. Additionally, actively exploring new application areas and developing multi-parameter imaging protocols and software specifically for PET/MR analysis will be key areas of future research. Through these efforts, the application effectiveness of PET/MR in medical imaging can be further enhanced. It is anticipated that PET/MR will become a highly valuable clinical diagnostic method, revolutionizing modern and future medical models. Simultaneously, PET/MR images integrate structural, functional, and molecular information, placing higher demands on the interpretive skills of nuclear medicine physicians.

The authors declare that they have no conflicts of interest.

Bibliography

1. Brown A, Kritharides L. Cardiovascular disease. *Heart Lung Circ* 2010; 19: 263.
2. Goldsborough E 3rd, Osuji N,Blaha M J.Assessment of Cardiovascular Disease Risk: A 2022 Update. *Endocrinol Metab Clin North Am* 2022; 51: 483-509.
3. Rischpler C, WoodardP. K.PET/MR Imaging in Cardiovascular Imaging. *PET Clin* 2019; 14: 233-44.

4. Quick HH. Integrated PET/MR. *J Magn Reson Imaging* 2014; 39: 243-58.
5. Senders M L, Calcagno C, Tawakol A et al. PET/MR imaging of inflammation in atherosclerosis. *Nat Biomed Eng* 2023; 7: 202-20.
6. Farzaneh-Far A, Kwong RY. Cardiovascular PET/MR: We need evidence, not hype. *J Nucl Cardiol* 2017; 24: 1032-5.
7. Karakatsanis NA, Abgral R, Trivieri MG et al. Hybrid PET- and MR-driven attenuation correction for enhanced ^{18}F-NaF and ^{18}F-FDG quantification in cardiovascular PET/MR imaging. *J Nucl Cardiol* 2020; 27: 1126-41.
8. Nensa F, Schlosser T. Cardiovascular hybrid imaging using PET/MRI. *Rofo* 2014; 186: 1094-101.
9. Cardoso R, Leucker TM. Applications of PET-MR Imaging in Cardiovascu lar Disorders. *PET Clin* 2020;15: 509-20.
10. Lau JM, Laforest R, Nensa F et al. Cardiac Applications of PET/MR Imaging. *Magn Reson Imaging Clin N Am* 2017; 25: 325-33.
11. Naeger DM, Behr SC. PET/MR imaging: current and future applications for cardiovascular disease. *Magn Reson Imaging Clin N Am* 2015; 23: 95-103.
12. Barrio P, López-Melgar B, Fidalgo A et al. Additional value of hybrid PET/MR imaging versus MR or PET performed separately to assess cardiovascular disease. *Rev Esp Cardiol (Engl Ed)* 2021; 74: 303-11.
13. Bergquist PJ, Chung MS, Jones A et al. Cardiac Applications of PET-MR. *Curr Cardiol Rep* 2017; 19: 42.
14. Rischpler C, Nekolla SG. PET/MR Imaging in Heart Disease. *PET Clin* 2016; 11: 465-77.
15. Schindler TH. Cardiovascular PET/MR: "Not the end but the beginning" *J Nucl Cardiol* 2017; 24: 1098-100.
16. Chen W, Jeudy J. Assessment of Myocarditis: Cardiac MR, PET/CT, or PET/MR? *Curr Cardiol Rep* 2019; 21: 76.
17. Shah SN, Oldan JD. PET/MR Imaging of Multiple Myeloma. *Magn Reson Imaging Clin N Am* 2017; 25: 351-65.
18. Hervier E, Glessgen C, Nkoulou R et al. Hybrid PET/MR in Cardiac Imaging. *Magn Reson Imaging Clin N Am* 2023; 31: 613-24.
19. Ripa RS, Pedersen SF, Kjær A. PET/MR Imaging in Vascular Disease: Atherosclerosis and Inflammation. *PET Clin* 2016; 11: 479-88.
20. Chowdhary A, Garg P, Das A et al. Cardiovascular magnetic resonance imaging: emerging techniques and applications. *Heart* 2021; 107: 697-704.