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Review

Generator-produced rubidium-82 positron emission tomography myocardial perfusion imaging—From basic aspects to clinical applications

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Summary Cardiovascular disease is the leading cause of death in modern industrialized countries with an aging population. This fact has fueled the need for innovative diagnostic testing intended to improve coronary artery disease (CAD) patient care. Detection of myocardial ischemia using myocardial perfusion imaging (MPI) plays an important role for CAD diagnosis and the prediction of future risk of cardiovascular events. Positron emission tomography (PET) MPI has high diagnostic accuracy and can estimate regional myocardial blood flow (MBF) in patients with CAD. Rubidium-82 (^{82}Rb) is a generator-produced PET myocardial perfusion tracer and has been widely used in North America in clinical practice. ^{82}Rb PET has recently become available in some cardiovascular centers in Europe and Japan. Clinical trials are expected in both regions. ^{82}Rb PET has high diagnostic accuracy and recent data have shown its prognostic value. Thus, ^{82}Rb PET would greatly contribute to CAD patients' care. ^{82}Rb PET can also be used to quantify MBF.

This review describes the current status of ^{82}Rb MPI from basic principles to clinical implications. This paper also highlights the recent development of MBF quantification using ^{82}Rb PET.

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Introduction

Coronary artery disease (CAD) continues to be a major cause of death both in modern industrialized countries and in developing countries. However, recent developments of coronary risk interventions have significantly reduced the risk of cardiovascular events. Thus, it is desirable to develop accurate and widely available noninvasive diagnostic testing to detect high-risk patients (vulnerable patients) [1].

The role of any diagnostic imaging test is to enhance the physician's decision-making process so as to improve symptoms and outcomes in patients with CAD. Techniques for evaluating myocardial perfusion are important for identifying patients with CAD and for predicting their future cardiovascular events. Thus, physiological information greatly contributes to strategy management in patients with CAD and subjects with various coronary risk factors.

The increasing numbers of patients with CAD necessitate the development of simple and widely available diagnostic techniques. Positron emission tomography (PET) represents an advanced nuclear imaging technology using molecular probes to understand the physiological process [2]. In the past, clinical use of cardiac PET has been limited by the requirement for an expensive, on-site cyclotron for radioisotope production as well as expensive PET scanners. However, the development of less expensive PET/computed tomography (PET/CT) cameras and the increased use of PET for oncology imaging have resulted in a wider clinical application of cardiac PET. More than 1000 PET and PET/CT scanners have been installed in North America [3], and currently there are nearly 200 PET centers in Japan. Rubidium-82 (^{82}Rb) is a PET myocardial perfusion tracer that is produced with a strontium-82 (^{82}Sr)/^{82}Rb generator and is widely used for the diagnosis of CAD in centers without immediate access to an on-site cyclotron [3,4]. Therefore, ^{82}Rb perfusion studies could be applied in larger populations [5,6].

The US Food and Drug Administration (FDA) approved ^{82}Rb generators for clinical use in 1989. US Medicare reimbursement began in 1995 [7] and is now approximately $1500 per rest-stress study. We estimate that there are currently about 120 sites where ^{82}Sr/^{82}Rb generators are in use in the USA. In Canada, The Ottawa Heart Institute manufactured a ^{82}Rb generator in 1999 and Health Canada approved its investigational use in 2003. In response to the shortage of Technetium-99m (^{99m}Tc) in 2009, the ARMI (Alternative Radiopharmaceuticals for Medical Imaging) trial will support implementation of ^{82}Rb PET in 10 new centers across Canada in 2010. To the best of our knowledge, the first ^{82}Rb human study published outside of North America was published in Japan by Manabe et al. [8]. Recently, some cardiovascular centers in Europe and Japan have initiated ^{82}Rb studies [8,9]. Thus, ^{82}Rb could be available worldwide in the near future.

Measurement of regional myocardial blood flow (MBF) permits the evaluation both of the physiological significance of coronary lesions and of vascular function in subjects with coronary risk factors [2,10]. PET MBF quantification is conducted mainly using ^{15}O-labeled water and ^{13}N-ammonia [2,10—12]; however, ^{82}Rb can also be used to estimate regional MBF using appropriate mathematical models [8,13—15].

^{82}Rb tracer characteristics

Rubidium has been studied in the context of myocardial perfusion since the late 1950s [16]. Rubidium is rapidly extracted from the blood and is taken up by the myocardium in relation to myocardial perfusion, which requires energy for myocardial uptake through Na/K-ATPase similar to thallium-201 [17]. Most recently introduced rubidium-82 (^{82}Rb) can generate a clear perfusion image, similar to conventional single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) because ^{82}Rb is an extractable tracer. Cell membrane disruption may cause rapid washout of ^{82}Rb from the tissue and ^{82}Rb can identify viable myocardium [18]. In animal models, the first-pass extraction fraction is 50—60% at rest and uptake decreases with increased flow (Fig. 1) [19—21].