Prevalence and nature of extracardiac findings in PET/CT myocardial perfusion imaging

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The superior diagnostic performance of positron emission tomography (PET) myocardial perfusion imaging (MPI) over single photon emission computed tomography (SPECT) MPI, the robust ability to quantify myocardial blood flow by PET and its lower radiation exposure, are leading to the increased adoption of PET for epicardial and microvascular coronary artery disease evaluation.[1] This is further supported by the 2021 multisocietal guideline document for the evaluation and diagnosis of chest pain which provided a class I recommendation for MPI in intermediate-high risk patients with stable chest pain, and a class IIa recommendation for choosing PET over SPECT for MPI, when PET is available.[2] In parallel, PET hardware has significantly evolved.[3] PET cameras detect paired 511 keV photons, localized using the coincidence detection principle. However, given both photons must be detected, the entire path they travel and the signal attenuation induced by soft tissue must be accounted for and corrected, i.e., attenuation correction (AC) implemented. Historically, AC for PET was done by radionuclide (^{68}Ge/^{68}Ga PET or ^{137}Cs SPECT) transmission rod sources circling around the patient to collect photon attenuation maps.[4] These have since been replaced by computed tomography (CT)-based attenuation in contemporary scanners given faster data acquisition and lower noise attenuation maps, among other improvements, further compounded by the additive anatomic and diagnostic information provided by CT.[5]

Imaging findings during PET/CT MPI that are not (cardiac) perfusion-related can be divided into two categories: extracardiac radiotracer uptake, and cardiac and extracardiac CT findings. Societal documents recommend that all reports include a section detailing these findings.[6] Indeed, there is a growing body of evidence underscoring the frequency and importance of these observations that require a systematic reading strategy by the interpreting physician as well as an understanding of clinical ramifications such as downstream testing.[7]

Evaluation of the extracardiac uptake of myocardial perfusion radiotracers necessitates a brief overview of their mechanisms of uptake (Figure 1). ^{15}O-water is freely diffusible across plasma membranes and has a theoretical extraction fraction of 100%. ^{13}N-ammonia also freely diffuses across the plasma membrane, gains a charge during that process to become ^{13}N-ammonium, which in turn reacts with glutamate to become ^{13}N-glutamine that remains trapped intracellularly. ^{82}Rb-chloride is a K^+ analog that predominantly requires active transport across the plasma membrane via the

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Na^{+}/K^{+}-ATPase pump to enter the cell. All these processes readily occur outside cardiomyocytes, laying the foundation for the extracardiac uptake and assessment of these perfusion radiotracers. Expansion of these observations to ^{18}F-flurpiridaz, a novel PET perfusion radiotracer that has undergone phase III evaluation,[8–10] is amenable to myocardial blood flow quantitation,[11–13] and is being presented to regulatory bodies for adoption in clinical practice, will be of further interest. ^{18}F-flurpiridaz has a very rapid uptake by cardiomyocytes and slow washout due to high binding affinity to mitochondrial complex-I (nicotinamide adenine dinucleotide [NADH]:ubiquinone oxidoreductase).[14] Given the near ubiquitous presence of mitochondria in multicellular eukaryotic organisms – with the notable exception of erythrocytes – 'foci' of extracardiac uptake with this perfusion radiotracer, similar to ^{15}O-water, ^{13}N-ammonia, and ^{82}Rb-chloride, are anticipated.

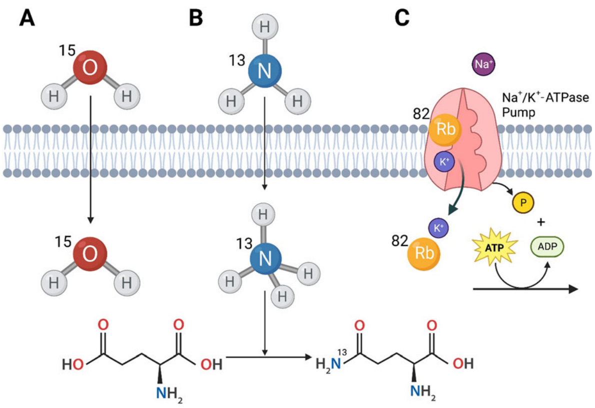

Figure 1. PET/CT MPI Radiotracers and Mechanisms of Uptake. (A) ^{15}O-water is freely diffusible across plasma membranes. (B) ^{13}N-ammonia is freely diffusible across plasma membranes and gains a charge to become ^{13}N-ammonium. In the cytoplasm, it transforms to ^{13}N-glutamine and remains trapped intracellularly. Another, likely minor mechanism of uptake has been proposed to occur via the Na^{+}/K^{+}-ATPase pump (not illustrated). (C) ^{82}Rubidium is a potassium analog and enters the cell through active transport via the Na^{+}/K^{+}-ATPase pump.

Although ^{13}N-ammonia was the first PET radiotracer developed for MPI,[15,16] it requires an on-site or very nearby cyclotron to be produced, limiting its widespread availability. In routine clinical practice, ^{82}Rb-chloride is the predominant PET MPI radiotracer used, in large part due to its on-site availability from generators where it is eluted from its parent compound ^{82}Sr. Whereas ^{15}O-water is used in Europe for PET/CT MPI, it is not approved by the U.S. Food and Drug Administration for clinical use.

In the present study by Jochumsen et al. published in the *Journal of Nuclear Cardiology*,[17] the authors

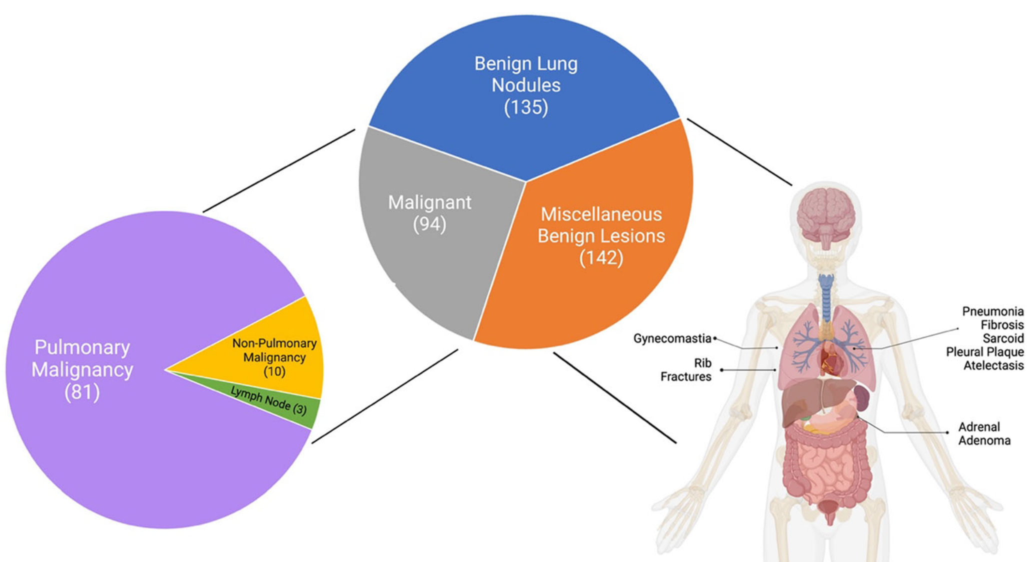

Figure 2. Distribution of Extracardiac Findings with ^{15}O-water. Of the n = 371 patients (13% of total) who demonstrated extracardiac uptake of ^{15}O-water, n = 94 had findings concerning for malignancy. By far the most common findings, either malignant or benign, were lung nodules which accounted for n = 216 of the extracardiac findings. Of the benign lesions, common findings included lung nodules, pneumonia, and atelectasis. Observations previously associated with the response to vasodilator stress, such as splenic 'switch-off' or increased skeletal muscle perfusion, are not depicted.

Table 1. Previous Studies on Incidental Findings in PET/CT MPI

Study	Reference	Study Population	Patient Numbers	Types of Extracardiac Manifestations (n)
^{13}N-ammonia				
Kan et al., 2017	18	All patients referred for PET/CT MPI	1397	Clinically Relevant Incidental Findings (248) Hiatal Hernia (86) Gallstones (52) Pulmonary Nodules (49) Enlarged Lymph Nodes (33) Concern for Malignancy (27) Nephrolithiasis (7)
^{82}Rb-chloride				
Mirpour et al., 2011	19	All patients referred for PET/CT MPI	406	Incidental Findings (67) Benign (59) Malignant (8)
He et al., 2019	20	Veterans referred for PET/CT MPI, comparison of cardiologist and radiologist interpretations	771	Incidental Findings (378) Lung Nodules (149) Hiatal Hernia (69) Extracardiac Mass (7)
Oldan et al., 2022	26	Patients diagnosed with breast or lung cancer within 60 days of PET/CT MPI	63	Lung Cancer (36) Breast Cancer (17)

determined the frequency and nature of extracardiac findings associated with ^{15}O-water uptake as observed during ^{15}O-water PET/CT MPI (Figure 2). All patients were scanned at rest and during pharmacologically induced hyperemia with a 6-min infusion of adenosine (0.14 mg/kg/min). The scans were 4-min dynamic acquisitions, initiated at the same time as the infusion of 400 MBq ^{15}O-water. The investigators evaluated n = 2963 consecutive patients using reports generated during clinical reads with summed PET images (as opposed to parametric images) in a single center. 13% of the reports indicated coincidental findings, of which appr. 1/3 were considered benign, 1/3 unchanged lung nodules, and 1/4 potential malignancies. Of note, potential malignancies were categorized as 86% new/unknown lung nodules or ground glass opacities, 9% highly suspicious of malignancy, and 3% enlarged lymph nodes. Importantly, in nearly all cases, extracardiac PET radiotracer uptake was corroborated by the attenuation CT scan, highlighting further the importance of hybrid imaging. The sole 'discrepant' case was due to differences in field of view between PET and CT.

Malignant lesions that were detected with increased ^{15}O-water uptake included lung cancer, lymphomas, breast cancer, and metastases of abdominal tumors. Non-malignant pathologies included lung findings such as pneumonia and fibrosis, pleural plaques, as well as sarcoidosis and rib fractures. The authors note that with few exceptions, the extracardiac uptake of ^{15}O-water was identical between rest and adenosine stress. Overall, these findings led to downstream testing in 4% of patients, most often a high-resolution CT scan as first line, and in some cases biopsy and/or ^{18}F-FDG PET/CT evaluation.

Previous studies analyzed the prevalence of extracardiac findings observed during ^{13}N-ammonia and ^{82}Rb-chloride PET/CT MPI, derived for the most part from the CT attenuation scans (**Table 1**). Kan et al.[18] reported their experience with ^{13}N-ammonia PET/CT in n = 1397 patients. Extracardiac findings were detected on low-dose attenuation CT. Clinically relevant / potentially relevant findings included lung nodules, enlarged lymph nodes, malignancies, and metastatic lesions. This study is noteworthy due to its significant proportion of females (47% of the study population). Mirpour et al.[19] included n = 406 patients who underwent ^{82}Rb-chloride PET/CT MPI, and observed n = 67 incidental findings. Of those, n = 8 were malignant. He et al.[20] completed the largest case series analyzing attenuation CT scans in ^{82}Rb-chloride PET/CT MPI in the veteran population; 96.2% were male, and 72.9% had a history of smoking. Of the n = 771 patients that were analyzed, n = 378 patients (49%) had incidental findings when interpreted by the radiologist, with the most common findings being pulmonary nodules and aortic aneurysms.

Whether the following parameters may affect the prevalence of extracardiac radiotracer uptake, and the characteristics of associated findings, will require further evaluation: positron range, radiotracer half-life, myocardial extraction fraction, rest vs. stress image acquisition, exercise vs. pharmacological stress, and finally the type and protocol of pharmacological stress.[21–25] On the other hand, CT-based extracardiac findings observed in PET/CT MPI will be similar regardless of the radiotracer used, and more dependent on the hardware and image acquisition techniques, including mA (rate at which electrons flow through the X-ray tube and X-rays are produced) x time, kV (energy of the X-rays), gantry rotation time, pitch, slice thickness, and field of view.

The article by Jochumsen et al. expands our understanding of extracardiac and incidental PET/CT MPI findings by providing the first observations with ^{15}O-water, and is thus an important addition to this field. Future studies should seek to systematically compare findings in PET/CT MPI with (i) extracardiac ^{18}F-FDG uptake to assess inflammatory and/or malignant processes that may be detected by the PET MPI radiotracer, (ii) high-resolution CT to determine the accuracy of cardiac and extracardiac CT findings observed during PET/CT MPI, and (iii) in a subset of patients – ideally – validation against the reference standard of tissue biopsy. Finally, machine learning to improve the quality of CT transmission scans may further enhance diagnostic accuracy when assessing extracardiac findings.

As our knowledge in this field continues to grow, nuclear cardiology interpreting physicians should be aware of the possibility of these findings, understand their potential significance, seek additional input as needed, and be well-versed in the interpretation of diagnostic observations outside of PET MPI.[7]

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Disclosures

None.

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