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Long Axial Field of View PET/CT: Technical Aspects in Cardiovascular Diseases

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Positron emission tomography / computed tomography (PET/CT) plays a pivotal role in the assessment of cardiovascular diseases (CVD), particularly in the context of ischemic heart disease. Nevertheless, its application in other forms of CVD, such as infiltrative, infectious, or inflammatory conditions, remains limited. Recently, PET/CT systems with an extended axial field of view (LAFOV) have been developed, offering greater anatomical coverage and significantly enhanced PET sensitivity. These advancements enable head-to-pelvis imaging with a single bed position, and in systems with an axial field of view (FOV) of approximately 2 meters, even total body (TB) imaging is feasible in a single scan session. The application of LAFOV PET/CT in CVD presents a promising opportunity to improve systemic cardiovascular assessments and address the limitations inherent to conventional short axial field of view (SAFOV) devices. However, several technical challenges, including procedural considerations for LAFOV systems in CVD, complexities in data processing, arterial input function extraction, and artefact management, have not been fully explored. This review aims to discuss the technical aspects of LAFOV PET/CT in relation to CVD by highlighting key opportunities and challenges and examining the impact of these factors on the evaluation of most relevant CVD.

Introduction

At present, positron emission tomography / computed tomography (PET/CT) plays an important role in the evaluation of several cardiovascular diseases (CVD). In the field of ischemic heart diseases (IHD), such as coronary artery disease (CAD), it has been demonstrated that PET/CT improves the diagnosis and predicts patients' prognosis more accurately, primarily through noninvasive quantitative evaluation of myocardial blood flow (MBF) and coronary flow reserve (ratio of MBF in stress over MBF at rest) (CFR).1 These values have also been shown to act as independent prognostic makers of major adverse cardiac events (MACEs).[2,3] However, in other types of CVD, such as

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infiltrative (e.g. amyloidosis, sarcoidosis), infectious (e.g. endocarditis), or inflammatory (e.g. vasculitis) diseases, cardiac PET/CT is not used routinely. Moreover, PET/CT protocols implemented in these CVD have been performed with the use of short axial field of view (SAFOV) scanners and PET/CT is in some indications not recommended as the first study modality in societies guidelines.[4-6]

Long axial field of view (LAFOV) PET/CT scanners represent the current state-of-the-art clinical imaging systems. These recently developed advanced scanners provide a larger anatomical coverage and a significant increase in PET sensitivity, allowing head-to-pelvis imaging within a single bed position, or even total body (TB) imaging in case of systems with a sufficient long axial field of view (FOV) (i.e. 2 meters). This is a substantial improvement over the conventional (SAFOV) approach in which continuous bed motion, multiple bed positions, or step-and-shoot techniques are used.7 The development of LAFOV scanners was based on studies that demonstrated that increments in axial FOV led to parallel increases in noise-equivalent count rates.[8,9] Currently, various LAFOV systems are available commercially, in particular the uEXPLORER (United Imaging Healthcare, Shanghai, China, axial FOV=196 cm), and the Biograph Vision Quadra PET/CT (Siemens Healthineers, Erlangen, Germany, axial FOV=106 cm). Most recently, some vendors have proposed scalable PET/CT devices, offering configurations that achieve LAFOV coverage, for instance, the Omni Legend (General Electric Healthcare, Chicago, IL, USA, axial FOV=128 cm) and the uMI Panorama GS (United Imaging Healthcare, Shanghai, China, axial FOV=148 cm).[8,10-12] Finally, some devices, such the PennPET Explorer (University of Pennsylvania, axial FOV=142 cm), have been developed by academic institutions for research purposes, although not available commercially yet.

For the evaluation of CVD, the limitation in axial coverage of SAFOV devices precludes single scan evaluation of all regions of interest in heart diseases with systemic involvement, systemic diseases with cardiac involvement, and the interaction/connection between the heart and other organs.13 Consequently, the availability of LAFOV scanners has introduced new technical horizons for research and routine clinical applications in CVD. LAFOV PET enables simultaneous imaging of the entire body (at least head to pelvis) and allows for studying the complex interplay between the cardiovascular system and other organs (e.g., kidneys, liver, lungs, brain or gut).[1] Moreover, the higher sensitivity and improved count statistics of LAFOV systems allow for kinetic modelling of various organs, which provides quantitative physiological measurements that go beyond suboptimal semi-quantitative parameters (e.g. target-to-background ratios [TBR], standardized uptake values [SUV], etc.). As such, LAFOV devices could enhance the assessment of medical drug (bio) distribution and therapy evaluation. Furthermore, advantages in sensitivity and statistics allow for a reduction in scan time, while preserving diagnostic accuracy. Alternatively, the injected dose of radioactivity can be lowered while maintaining image quality, which is particularly relevant when considering pregnant women or children. Specific combinations of the previously described advantages could allow dual radiotracer imaging or imaging of slow biological processes, permitting the study of important (patho) physiological mechanisms, such as the immune response.[14] Finally, LAFOV allows for the extraction of an image-derived input function (IDIF) from large vascular structures when evaluating other organs relevant for CVD apart from the heart, particularly the brain, where the aorta or other large vessels are not within the FOV when SAFOV scanners are used.[15] Leveraging all technical capabilities of LAFOV PET/CT scanners opens the possibility of a broader evaluation of the cardiovascular system, focusing on a systemic approach, rather than solely on the heart.[16]

The potential of LAFOV PET/CT scanners in CVD has recently been demonstrated.[13,16] However, several technical considerations, ranging from LAFOV system procedures in CVD to the complexity of data processing, arterial input function extraction, or handling of artefacts (e.g., motion, attenuation), have not been fully discussed, yet. This review aims to describe the technical aspects of LAFOV PET/CT related to CVD, by presenting the main opportunities and challenges, and evaluating how these issues impact the evaluation of the most relevant CVD.

Technical Issues

Table 1 presents a summary of the main technical challenges of LAFOV PET when compared with SAFOV PET. In addition, possible solutions for these challenges are depicted. In the following paragraphs, a thorough discussion of each technical issue is presented.

Infrastructure and Hardware

Regarding infrastructure, the potentially higher throughput of patients scanned with LAFOV scanners necessitate well-designed patient areas. These facilities should accommodate higher patient volumes efficiently with ample space for waiting, changing and preparation rooms.[17] The camera room must support the substantial size and weight of LAFOV scanners, potentially requiring structural modifications. Adequate air-conditioning and water coolant supply are necessary to manage the heat generated by the scanner. Adjacent rooms for data processing and storage are also needed. A robust electricity supply is essential to support the high-power requirements of LAFOV scanners, possibly requiring an upgrade.[18,19]

LAFOV PET/CT systems generate large volumes of data. For instance, a single scan may produce 40-50 gigabytes (GB) and dynamic acquisitions can result in several terabytes (TB) of data. Therefore, robust and scalable networking and storage solutions are required. Hospital information technology (IT) may find it complicated to handle this load, necessitating dedicated storage infrastructures. Solutions to deal with these issues are implementing a petabyte-scale Redundant Array of Independent Disks (RAID) in the equipment room as an effective local buffer, which facilitates rapid data

Table 1 Technical Challenges in LAFOV PET

Technical Aspect	Added Challenge in LAFOV Compared to SAFOV	Possible Solutions
Infrastructure	- Substantial increment in weight and size - Production of more heat while functioning - Higher electric requirements - Auxiliary equipment (ideally including an on-site cyclotron)	- Perform any required structural modification to the camera room - Ensure adequate air-conditioning and water coolant supply - Update electric installations to ensure a robust electricity supply - Evaluate the necessity of an on-site cyclotron or a dedicated mini-cyclotron
Hardware	- Generation of bigger data volumes - Transferring bigger data volumes - Need for more robust servers for postprocessing, image viewing, and data analysis	- Update network and storage solutions. Install dedicated data storage devices. - Install high-speed fiber optic connections to prevent bottlenecks during data up-/off- loading - A petabyte-scale RAID in the camera room and high-speed network connections facilitates the handling of LAFOV data
Software	- Few software packages can handle LAFOV data - Need for multiorgan compartment modelling - Need for TB organ segmentation - Separation algorithms (or similar) are needed if dual- or multiradiotracer imaging is intended	- Encourage vendors to develop and/or update software packages for LAFOV PET image processing - Test for the most appropriate organ- and tissue-models - Use existing pipelines for TB CT segmentation (TotalSegmentator, SEQUOIA, Moose, etc.) - Set prospective research protocols aiming to explore the feasibility of multi/dual-radiotracer LAFOV imaging
Computational Power	- Data to handle is considerably larger - Higher amounts of RAM needed for image reconstruction and processing	- Assure workstations and software meet technical requirements - Optionally, allow access to GPU- or AI-boosted environments
Input Function	- Sampling (either manual or with an on-line system) is more difficult - Longer arterial/venous lines are associated with more delay and dispersion	- Use IDIF or PBIF approaches for input-function extraction in LAFOV PET - Evaluate if corrections for delay and dispersion are needed depending on the radiotracer and protocol
Radiotracer Kinetics	- Only [^{15}O]H_2O is suitable for multiorgan imaging (freely diffusible and no need for PBR/PPF corrections) - Tissue-specific kinetics in organs other than the heart/brain, are yet unknown for radiotracers used in CVD	- Test for the feasibility of LAFOV multiorgan imaging in CVD with the use of other radiotracers than [^{15}O]H_2O - Evaluate multiorgan kinetics of all relevant radiotracers in CVD
Attenuation Correction and CT	- Increase in axial field of view leads to a higher risk of attenuation mismatch between PET and CT data - Most methods for AC are focused and developed on SAFOV scanners	- Careful evaluation of the accuracy of PET/CT co-registration along the field of view - Simultaneous acquisition of intrinsic background radiation from lutetium oxyorthosilicate (LSO) detectors data with PET emission data may help reduce misregistration errors[157] - Test currently available methods for AC in LAFOV PET (respiratory-gating, IACT, DeTransUnet, etc.)
Motion Correction	- An increased axial coverage leads to a higher probability of motion artifacts - Most methods for MC are developed for SAFOV devices, correcting for motion only in a specific organ/region - Few methods for performing MC in dynamic PET scans, practically none for MC in dynamic LAFOV PET	- Careful inspection of final images and quantitative values to timely detect any significant motion artifact - Propose and evaluate pipelines for TB MC in LAFOV PET - Probably feasible to simultaneously apply different SAFOV MC tools in LAFOV PET

RAID, Redundant Array of Independent Disks; LAFOV, long axial field of view; TB, total body; RAM, rapid access memory; GPU, graphics processing unit; AI, artificial intelligence; PBR, plasma-to-whole blood ratio; PPF, plasma parent fraction; CVD, cardiovascular diseases; AC, attenuation correction.

transfer to the reconstruction workstation. Furthermore, older data can be offloaded periodically to centralized hospital storage systems via high-speed network connections (e.g. multiple 10 GBps lines).[20,21] In addition, servers used for viewing, postprocessing and data analysis should be designed to handle these substantial amounts of data. Furthermore, the high photon count rates of LAFOV systems demand efficient data transfer to enable timely clinical analysis.[22] In this context, high-speed fiber optic connections (e.g., 40 GBps) are essential to prevent bottlenecks during data offloading. High-capacity and high-speed solutions are vital for managing the data deluge and enabling effective data processing and analysis.[18,20,22,23]

Supporting LAFOV scanners requires various auxiliary equipment, including radiotracer production facilities, compatible gating equipment, and blood sampling systems. Onsite cyclotrons may be needed for higher radiopharmaceutical production due to the faster scanning capabilities and increased patient throughput of LAFOV PET/CT systems.[22] However, this increased sensitivity could also revive the use of shorter-lived radiotracers like ^{11}C and ^{15}O, despite the current popularity of ^{18}F-radiotracers.[24] Blood sampling systems also face challenges such as difficulties in accessing radial arteries and increased dispersion in longer on-line sampler tubing. Noninvasive image derived input functions (discussed below) could offer solutions. Integrating all the specific needs regarding auxiliary equipment into the workflow of TB examinations, ensures efficient and effective scanner operation.[19,25]

Software

The extended coverage of LAFOV PET enables the simultaneous assessment of multiple organs, offering unique opportunities to study the interplay between heart, vessel walls and other organs for optimal cardiovascular health.[13] Radiotracer kinetic models, which provide mathematical descriptions of the radiotracer's fate in the human body, are essential for quantifying tissue kinetics and extracting physiologically relevant parameters from dynamic PET data. For instance, modelling of dynamic $[^{15}O]H_2O$ PET data typically employs a 1-tissue compartment model. However, additional factors should be considered for accurate TB modelling, such as proper delay and dispersion corrections,[26] and dual input functions for the lungs and liver.[27] Other radiotracers used in CVD, such as ^{82}Rb, are described by either 1-tissue[28] or 2-tissue compartment models,[29] whilst [^{18}F]FDG [18] and $[^{13}N]NH_3$[30] require a 2-tissue compartment model. The main challenge for compartmental modelling of LAFOV data is the need to use organ- and tissue-appropriate models, which is especially challenging for parametric imaging. Other methods have also been proposed for modelling radiotracers, including basic function, principal component, independent component, factor, spectral, cluster, or heterogeneity analysis.[31] Multiorgan segmentation tools are also essential to perform kinetic modelling of cardiovascular data across the entire human body. Although there is no generally accepted LAFOV PET segmentation tool available yet, various pipelines have been developed using CT-based total body segmentation methods, such as TotalSegmentator,[32] MIWBAS,[33] Moose,[34] DAFS[35] and SEQUOIA for aortic PET/CT studies.[36] Typically, these approaches perform either CT-based total body segmentation followed by clustering of TB PET images[2] or PET-CT co-registration with subsequent CT segmentation. The lack of standardization of multiorgan segmentation can represent a limitation, as the accuracy of PET segmentation relies on the quality of CT-PET co-registration and is affected by different factors (e.g. patient motion, respiratory motion, differences in image resolution between PET and CT data).

The high sensitivity and noise-equivalent count rate (NECR) of LAFOV PET/CT systems have opened up new opportunities for dual-radiotracer and even multiradiotracer imaging.[7] This technique allows simultaneous evaluation of different pathologic processes by administration of distinct radiotracers within a single scan session, providing complementary information that would otherwise require multiple scans.[37] For example, vascular inflammation and perfusion can be explored simultaneously by the injection of radiotracers specific for calcification activity ([^{18}F] NaF,[38,39] fibroblast activation ([^{68}Ga]-fibroblast activation protein inhibitor, FAPI),[40] or thrombus formation ([^{18}F]-glycoprotein 1)[40] in combination with radiotracers for measuring perfusion (i.e. $[^{15}O]H_2O$, $[^{13}N]NH_3$, ^{82}Rb, [^{18}F]flurpiridaz). However, to extract individual information for each radiotracer, separation algorithms for simultaneous dual radiotracer (multiradiotracer) need to be developed and validated in clinical settings.

Computational Requirements

LAFOV PET/CT scanners consist of a large number of rings (i.e. 320 for the Siemens Biograph Vision Quadra) and most also register time-of-flight information, making data sizes very large (e.g. several TB of raw data for a 65-minute dynamic FDG PET scan). In this setting, image reconstruction is computationally challenging and requires substantial amounts of rapid access memory (RAM). Particularly, when parametric images based on kinetic models are generated, several hundred gigabytes of RAM are demanded.

At the image level, the high dimensionality of LAFOV PET images also leads to higher requirements for image analysis software and workstations. For instance, with typical image dimensions of 440×440×708 voxels, each 3D PET image can contain over 100 million voxels and have a file size of 100-250 megabytes. However, in case of dynamic scans with many frames, the total amount of data can reach several TB. Existing software for image processing was not developed for these extremely large datasets and may not work consistently enough as in SAFOV. Sometimes, when uploading TB images, processing software packages may even break down, as most of them have not been developed/updated for handling this type of scans. Furthermore, the necessity of fitting multiple compartmental models in LAFOV parametric imaging,[41] also requires a minimum of computational power.

Motion detection, estimation, and correction also present a significant obstacle as discussed in a later section.

Artificial intelligence (AI) methods may be the key to transform the large datasets of LAFOV PET/CT into meaningful insights. A recent review focused on the role of AI in extracting meaningful information from LAFOV PET image data.[42] Current applications include AI-driven segmentation (MOOSE[34] and TotalSegmentator[43]) and detection tools, for instance for aortic wall uptake in systemic inflammations. Furthermore, since the PET dose can be reduced significantly with LAFOV PET, AI may have a role in both, improving further image quality for low-count PET scans,[44] and for ultra-low-dose CT (ULD-CT) acquisitions [45] (discussed in detail in the respective sections).

Input Function

For kinetic analysis, an accurately measurement of the delivery of the radiotracer to the tissue is essential.[46] The standard approach is the arterial input function (AIF), which involves serial and/or continuous blood sampling. Ideally, an on-line sampling system is used. In addition, a few manual samples are collected to determine the plasma-to-whole blood ratio (PBR) and the plasma parent fraction (PPF). This latter information is used to transform the sampler whole blood curve into a metabolite corrected plasma time activity curve (PTAC). In LAFOV scans, manual sampling is a challenge, as access to the patient is more difficult than for SAFOV PET. In most cases, unconventional longer venous lines are needed for injecting the radiotracer and pharmacological stressors (if needed), which are associated with more delay and dispersion.

To overcome the above-mentioned limitations, noninvasive approaches can be applied to obtain an input curve, e.g. an IDIF or a (scaled) population-based input function (PBIF).[47] The IDIF can be estimated using the image derived whole blood time activity curve (BTAC) by placing a volume-of-interest in a large vascular structure such as the aorta or left ventricle of the heart, which allows for an accurate measurement of the radioactivity concentration in whole blood. The BTAC is converted into a PTAC using the PBR and can be adjusted with the PPF, if necessary. This metabolite corrected PTAC is often referred to as IDIF. For radiotracers like $[^{15}O]H_2O$, which do not require any PBR or PPF correction, the IDIF can be extracted directly from the heart or aorta.[48] This IDIF method has already been used for several years in SAFOV scans for quantification of myocardial perfusion.[49] The appearance of LAFOV scans enables multi-organ blood flow quantification. In this setting, the possibility of deriving a plasma input function without blood sampling from the fitting of PTAC in different tissues has to be tested.[2]

PBIF offers another approach by utilizing population arterial input functions or IDIFs from representative subjects.[47] PBIF can provide a practical alternative when individual arterial sampling is not feasible, reducing patient discomfort and resource requirements. Therefore, it is crucial to validate PBIF for each specific radiotracer and patient population, potentially considering factors such as radiotracer characteristics and patient demographics, to ensure its accuracy and reliability.[50]

Kinetics of Blood Flow Radiotracers

The study of CVD by PET/CT relies on the use of different radiotracers that are highly extracted and/or accumulated in the myocardial and/or endothelial walls, allowing distinction of the myocardium/vascular endothelium from surrounding tissues. The most important radiotracer for measuring myocardial perfusion, generally accepted as the gold standard, is $[^{15}O]H_2O$. Its short half-life ($T_{1/2} = 2.1$ minutes) permits rapid sequential imaging, and this radiotracer has been used extensively for the evaluation of myocardial and cerebral blood flow.[51] Bergmann *et al.*[52] demonstrated that free water diffusion was modest, constant, and not affected by changes in flow. Hence, its tissue uptake relates solely to flow and, unlike ^{13}N-labeled ammonia ($[^{13}N]NH_3$) or Rubidium-82 (^{82}Rb), it is independent of transport mechanisms or metabolism. For perfusion imaging, especially in pathophysiological conditions, this is very attractive, as changes in myocardial metabolism or energy status will not affect flow estimates. Free diffusion of $[^{15}O]H_2O$ makes kinetic modelling straightforward, and commonly a 1-tissue compartment model is used in which the vascular space and tissue are considered together.[52] Intrinsic partial volume and spill-over corrections are included in the mathematical model, at least for the myocardium.[53] Myocardial viability has also been assessed with the use of $[^{15}O]H_2O$. Quantification of MBF in rest, perfusable tissue fraction, and perfusable tissue index have been validated against MRI for this purpose.[54]

Other radiotracers often used as surrogates of myocardial perfusion in dynamic PET studies are $[^{13}N]NH_3$ and ^{82}Rb. $[^{13}N]NH_3$ ($T_{1/2} = 9.8$ minutes) and the ammonium cation $[^{13}N]NH_4^+$ rapidly reach a dynamic equilibrium under physiologic conditions, resulting in a first-pass extraction fraction of >95% in the myocardium.[55] Several modelling strategies (both single and 2-tissue compartment models) have been developed to estimate perfusion while accounting for the incomplete metabolic trapping of the radiolabel in the myocardium.[56] In contrast, ^{82}Rb is a cation, which is actively transported into myocytes. Its short half-life ($T_{1/2} = 76$ seconds) allows for rapid imaging protocols, but also introduces problems for both image analysis as well as tracer kinetic modelling due to the high noise levels and the high energy of the emitted positron. Nonetheless, ^{82}Rb has been used extensively for the diagnosis of CAD. For full quantification of MBF with ^{82}Rb, the 1-tissue compartment model is used, including appropriate correction factors for partial volume effects and spill-over.[28] Interestingly, myocardial viability can be assessed using ^{82}Rb as well. In ischemic myocardium, cations such as potassium or rubidium leak out of the cell because of the inability of the ionic pumps to maintain the cell gradients. Initial studies suggest that ischemic myocardium has a diminished ability to trap rubidium and thus, increases in k_2 may indicate myocardial viability,[57] which requires application of a 2-tissue compartment model.

With the introduction of LAFOV PET, CVD can be evaluated using [^{15}O]H_2O dynamic imaging of all organs and tissues of interest simultaneously. This may be useful for the study of specific diseases. For instance, obstructive CAD shares the same pathophysiologic atherosclerotic process in arteries supplying the brain (i.e. cerebrovascular disease) as well as lower limbs (i.e. peripheral artery disease). In addition, patients with CAD commonly have more than 1 organ system involved.[2] Similarly, some diseases, such as diabetes, may induce microvascular dysfunction in the heart but also in other organs, such as the brain, eyes and kidneys.[58] Furthermore, CAD may affect the nervous system and, in turn, neurologic disorders may affect the cardiovascular system, i.e. the heart–brain axis.[58] Knuuti *et al.*[2] have shown the first proof of concept results of the interactions from the peripheral and central circuits in anxiety during adenosine-induced cardiac stress. Widespread inter-organ correlations in perfusion during stress become more focused during adenosine infusion, indicating a stronger interplay during pharmacologically induced stress. These observations highlight the need to explore the interplay of different organ systems, and the evaluation of perfusion by LAFOV PET can accommodate this need.

Attenuation Correction and CT

Attenuation correction (AC) is crucial for accurate PET imaging, as it accounts for the loss of annihilation photons due to interactions with the patient's body.[59] However, various artefacts can arise, leading to quantification errors with potentially compromised diagnostic accuracy, especially in CVD imaging.[60,61] Innovations in PET technology, including LAFOV scanners, have allowed for significant dose reductions. However, to maximize these benefits, equivalent efforts must be made to lower the radiation dose from CT scans, ensuring the overall safety and effectiveness of PET/CT imaging.[62,63] Recently, ULD-CT with tin filters in LAFOV PET/CT scanners has been proposed to minimize radiation exposure while maintaining PET image quality.[63]

A significant challenge in AC for PET imaging is the mismatch between PET emission data and the attenuation map, often due to respiratory motion or patient movement, which both can lead to severe artefacts, especially in CVD imaging where sharp attenuation gradients near the heart can mimic perfusion defects and cause misdiagnosis.[61,64] Various methods have been developed to address this issue, including respiratory gating,[64] cine-averaging CT techniques like Interpolated Average CT (IACT), [65] and deep learning approaches like DeTransUnet.[66] IACT interpolates between end-inspiration and end-expiration CT phases to better match respiratory averaged PET data, while DeTransUnet uses a 3D convolutional neural network with deformable transformer layers to estimate attenuation corrected PET images directly from nonattenuation corrected data. In addition, LAFOV PET scanners offer advantages such as shorter acquisition times, reduced motion artefacts, improved image quality, and lower radiation doses, but they also pose the challenge of potentially more severe artefacts from patient movement affecting a larger portion of the data. Methods like the simultaneous acquisition of intrinsic background radiation from lutetium oxyorthosilicate (LSO) with PET emission data may help to reduce co-registration errors.[67]

Other common artefacts in PET AC include those caused by metallic implants and contrast agents.[61,68-70] Metallic implants can lead to streaking artefacts and over- or underestimation of radiotracer uptake, depending on their density.[71] Contrast agents can also cause artefacts, necessitating careful inspection of nonattenuation corrected PET images.[72] Potential solutions to these artefacts include careful patient positioning, documentation of nonremovable metallic objects, and software-based artefact identification and correction algorithms.[61,71,73]

In summary, AC in CVD LAFOV PET is challenging like in SAFOV scanners, and although different methods offer potential solutions, they are more focused on SAFOV scanners. Further research is needed to develop accurate and reproducible AC methods that ensure reliable quantification and diagnostic accuracy in LAFOV PET.

Motion Correction and Cardiac / Respiratory Gating

The presence of motion artefacts is a long-standing problem in PET imaging, both caused by nonrigid (e.g. respiratory and cardiac motion) as well as by rigid motion (e.g. head movement, patient's gross body motion).[74] Specific characteristics of motion, such as periodicity (e.g. regular or irregular breathing), timing of occurrence (blood pool phase or tissue phase), or intensity (e.g. gradual increase in heart rate due to pharmacological stress or abrupt patient motion), can induce motion artefacts with effect on image quality and/or tracer quantification.[74,75] In comparison with SAFOV devices, the augmented axial FOV in LAFOV equipment would logically increase the chance of images being affected by motion somewhere along the field of view.

Two types of motion need to be addressed when working with PET imaging: i) motion occurring during the PET acquisition itself, and ii) motion between the AC maps and PET acquisition [attenuation-mismatch (discussed in the previous section)]. The impact of motion on image accuracy and diagnostic outcome is well-documented, with numerous motion correction (MC) methods proposed over the years.[60,76-85] However, many of these methods were developed for SAFOV scanners, which only cover a more restricted body region. The broader coverage of LAFOV PET/CT scanners introduces additional challenges, as MC must, ideally, handle motion from multiple body regions simultaneously. Another possible approach would be to apply different MC tools simultaneously to correct the motion present in the different organs/regions of interest. Nevertheless, currently, there are no TB MC methods available, and the feasibility of the use of several MC tools at the same time has not been tested.[74,86]

Specifically for CVD imaging with SAFOV PET/CT, specialized gating techniques are currently employed to enhance image quality and accuracy. Cardiac gating utilizes the ECG R-

wave to sort data into nearly motion-free cardiac phases, improving visualization and quantification of myocardial radiotracer uptake.[87,88] Respiratory gating synchronizes PET data acquisition with the patient's breathing cycle using external markers such as piezo-electric belts or infrared systems.[87,89] Optical motion tracking methods have also emerged as alternatives, employing cameras or sensors to monitor external markers on the patient's body. More recently, data-driven methods have replaced external markers and their associated limitations.[90] Despite these advancements, these techniques are still not widely available or routinely used for LAFOV PET/CT, mainly due to the previously discussed limitations in computational power, software availability, and patient access during the scan (in cases where external devices are used for acquiring ECG/breathing data).

Pre- and during-reconstruction approaches for MC have been developed and tested in recent years. For instance, a data-driven MC (DDMC) algorithm has been shown to accurately track and correct for myocardial wall rigid motion both in static and dynamic acquisitions in SAFOV PET/CT. Unfortunately, these methods have not yet been adapted or tested in LAFOV scanners, as computational power arises again as a major limitation when trying to use DDMC approaches, even in SAFOV devices.[91] While not having the advantages of DDMC methods, postreconstruction registration of dynamic PET images can be used to reduce misalignment between adjacent frames. Even though LAFOV PET frame alignment becomes more challenging compared with SAFOV frames, since it must simultaneously deal with complex motion in different body regions, open-source tools for fully automatic frame alignment in dynamic LAFOV PET imaging already exist.[92-94]

In contrast to these methods, the breath-holding (BH) technique offers a rapid alternative to MC. Traditional PET imaging often struggles with BH due to lengthy acquisition times. However, the high sensitivity of LAFOV PET/CT systems makes BH feasible.[95] Patients can hold their breath for approximately 20 seconds, facilitating the acquisition of high-quality thoracic images without the blurring effects of respiratory motion. This approach enhances the clarity of thoracic and cardiac structures, providing more accurate quantification measurements and thereby improving diagnostic confidence.[95] However, it may be challenging for patients with impaired respiratory capacity or difficulties in maintaining stillness.

Specific Disease-Based Technical Options

Table 2 summarizes the principal technical opportunities that LAFOV devices introduce for the study of some of the most relevant CVD. Below, a disease-based discussion of these technical opportunities is presented.

Coronary Artery Disease and Microvascular Coronary Dysfunction

Chronic coronary syndromes (CCS) are systemic diseases characterized by inflammation leading to atherosclerosis, which may affect multiple organs, including the brain and kidneys. The advent of LAFOV PET enables comprehensive evaluation of multiple organs in patients undergoing CCS examination. This allows for the simultaneous investigation of myocardial perfusion alongside cerebral and renal perfusion, amongst others.[96] Technological improvements implemented in LAFOV scanners facilitate accurate MBF quantification without the need for gating.[97]

Furthermore, as highlighted by Cherry *et al.*,[16,98] LAFOV PET makes it possible to calculate the percentage of cardiac output for various organs and derive vascular resistance for these organs simultaneously, which was not possible before. Considering the higher risk of adverse events in patients with diffuse atherosclerosis causing arterial stenosis throughout the body, simultaneous perfusion analysis of multiple organs can enhance patient management and outcome without increasing radiation exposure or scan duration.[99]

On the other hand, numerous studies have demonstrated that PET can noninvasively identify and characterize coronary microvascular dysfunction (CMD) by quantifying reductions in hyperaemic MBF and/or CFR.[100] Moreover, recent research indicates that microvascular dysfunction is a systemic condition, affecting multiple organs including the heart, brain and kidneys.[101] A systematic holistic approach is needed in future research and clinical care.

By analysing variations in local radiotracer extraction and tissue kinetics, LAFOV PET/CT facilitates the concurrent assessment of microvascular disease across vascular beds in all organs. Such an exhaustive assessment is crucial for accurately diagnosing and comprehensively understanding the underlying pathophysiology that appears to involve various regions and organ systems.[102,103]

Atherosclerosis

Atherosclerosis is a multiorgan disease affecting the entire body. There is still no imaging modality allowing for rapid diagnosis without increasing radiation dose, costs or scanning time. The absence of atherosclerotic processes in the heart does not preclude their presence in the brain, and vice-versa. Unfortunately, current imaging methods are organ-focused rather than body-focused. As evidence from cardiac studies indicates that myocardial infarction is likely caused by high-risk lesions,[104] significant efforts are being made to identify high-risk plaques responsible for stroke, myocardial infarction, and emboli in peripheral arteries. LAFOV PET/CT is the sole method capable of calculating atherosclerotic burden and identifying high-risk plaques, thereby increasing cardiovascular risk assessment accuracy.[105,106] Two PET radiotracers, [^{18}F]FDG and [^{18}F]NaF, have been used to investigate atherosclerotic burden.[107,108] [^{18}F]FDG and [^{18}F]NaF reveal inflammation and microcalcifications within arterial walls, respectively.[109] This technique allows visualization

Table 2 Technical Opportunities Available in LAFOV PET for the Main CVD

Cardiovascular Disease	Main Technical Options Brought by LAFOV Devices
Coronary Artery Disease / Coronary Microvascular Dysfunction	- Possibility to evaluate perfusion (blood flow measurements) throughout most body regions and/or organs and not solely the heart (multiorgan evaluation) - Feasible to simultaneously evaluate the interaction between the heart and other organs (evaluation of heart-organ axes) -Monitoring immune modulation in cardiac fibrosis[158]
Atherosclerosis	- Possibility to visualize active atherosclerotic plaques not only in major arteries but also in distal branches - Feasible to investigate thrombus formation in multiple organs (using [^{18}F]GP1 radiotracers)
Vasculitis	- Easier to perform dynamic and parametric PET imaging may enable a more robust assessment of vessel pathology for primary diagnosis, therapy monitoring and disease recurrence - Improved image quality allows PET imaging for low-count radiotracers [^{89}Zr-labeled monoclonal antibodies, radiotracers targeting T-cells (CD8) or immune-cell markers (IL-2 receptor, FAPI)]
Amyloidosis	- Possibility to image all organs in a shorter acquisition time and 1-bed position, alleviating patient discomfort - Possibility of serial evaluation of patients due to lower radiation burden for screening purposes and to evaluate therapy response - Theoretically, total body kinetic modeling and quantification of amyloid burden could allow to differentiate between the distinct variants of amyloidosis
Sarcoidosis	- Possibility to image all organs in a short acquisition time and 1-bed position, alleviating patient discomfort - Possibility to improve the accuracy in the selection of the biopsy site for diagnostic purposes - Possibility to evaluate therapy response by allowing serial evaluation of patients due to lower radiation burden
Infective Endocarditis	- Possibility to detect disseminated endocarditis across all body regions in a short acquisition time and 1-bed position - Possibility to improve the sensitivity for the diagnosis of prosthetic valve endocarditis - Possibility to improve the sensitivity for detecting native valve endocarditis, by improving the use of gating
Critically ill patients	- Feasible to incorporate LAFOV PET imaging in these patients due to the important reduction in scanning time - Feasible to routinely use LAFOV PET imaging within the critical care department due to reduction of staff radiation exposure

LAFOV, long axial field of view; CVD, cardiovascular diseases; GP, glycoprotein; Zr, zirconium; CD, cluster of differentiation; IL, interleukin; FAPI, fibroblast activator protein inhibitor.

of active atherosclerotic plaques, not only in major arteries, but also in distal branches. Despite slight discrepancies, both radiotracers are instrumental in detecting early-stage atherosclerosis, which is not feasible with another imaging method.[110]

LAFOV PET/CT may also help to increase the specificity of thrombus imaging. Knowing that high-risk plaques lead to thrombus formation and as a result to coronary thrombosis or cerebral infarction, noninvasive imaging may help to find a thrombus undetected by other diagnostic methods.[111] As previously shown, new radiotracers, e.g. [^{18}F]GP1 targeting activated platelet glycoprotein IIb/IIIa receptors, enabled thrombus detection while invasive coronary angiography could not visualize thrombus formation in the culprit lesion.[40] With the introduction of LAFOV PET/CT, investigation of thrombus formation in multiple organs becomes feasible, highlighting the potential of LAFOV PET/CT to become a leading imaging method, as it brings an opportunity to replace multiple diagnostic and imaging methods with a single scan.

Vasculitis

Vasculitis represents a heterogeneous group of diseases characterized by inflammation of vessel walls. More than 30 types of vasculitis have been reported,[112] and one of the most prevalent is giant cell arteritis (GCA),[113] in which T lymphocytes and macrophages infiltrate all layers of the arterial wall leading to vascular complications. These complications depend on the vessel involved. GCA, and other types of vasculitis such as Takayasu arteritis, or Kawasaki disease can lead to myocardial ischemia and infarction, but also cerebral ischemia.[114] A recent review by van der Geest *et al*. provides an overview of the advances in PET imaging of large vessel

vasculitis.[115] One key challenge in vasculitis described is the interpretation of [^{18}F]FDG PET uptake during glucocorticoid treatment and therapy monitoring. In addition, the limited spatial resolution of SAFOV PET scanners precludes evaluation of the smaller arteries.

LAFOV PET/CT scanners present opportunities by offering improved signal-to-noise ratio, enabling shorter scan durations, reduced motion artefacts and improved parametric imaging. Furthermore, LAFOV PET/CT may require different thresholds for semi-quantitative parameters like liver-normalized SUV compared with standard scanners, likely due to reduced noise.[116] A case report also demonstrated clear signs of GCA on LAFOV PET even with a 1-minute scan duration, highlighting the potential for shorter scans and reduced motion artefacts.[117] Finally, the possibility of performing dynamic PET, and generate parametric images (e.g. K_i) in LAFOV scanners, may provide a more robust assessment of vessel pathology compared with static [^{18}F]FDG PET, mainly by means of allowing evaluation of smaller arteries and better detection of "true" vessel wall uptake. Studies are ongoing to explore this potential using LAFOV PET/CT scanners

The higher signal-to-noise ratio in LAFOV scanners is particularly advantageous for low-count radiotracers such as ^{89}Zr-labelled monoclonal antibodies[118] and novel radiotracers with slower kinetics targeting CD8 molecules on T-cells.[119] Novel radiotracers targeting immune cell markers like IL-2 receptor,[120] CD8[119] and fibroblast activation protein radiotracers [121] may show promise in detecting GCA in the future.

Amyloidosis and Sarcoidosis

Infiltrative cardiomyopathies, such as amyloidosis and sarcoidosis, present unique challenges in diagnosis and treatment due to their systemic nature and involvement of multiple organs. Amyloidosis is characterized by protein misfolding and amyloid accumulation, whereas sarcoidosis involves the formation of noncaseating granulomas.[122,123] Although these diseases differ in pathogenesis, accurate diagnosis and determination of all potentially affected organs is essential for predicting prognosis and initiating optimal treatment in both conditions.[123-125]

PET/CT imaging offers the potential to detect early involvement across all organ systems in systemic amyloidosis.[126] In sarcoidosis, PET/CT allows for accurate disease staging and selection of biopsy sites.[127,128] In addition, PET is the preferred imaging modality for assessing therapy response in sarcoidosis and is anticipated to become pivotal in future therapy assessment in amyloidosis.[129,130]

Currently, TB PET is performed using SAFOV PET scanners by using multiple bed positions. In contrast, LAFOV scanners enable the simultaneous assessment of multiple organ systems within 1 bed position. The use of LAFOV PET could enhance diagnosis and follow-up in sarcoidosis and amyloidosis due to its higher sensitivity, which allows for shorter acquisition times or reduced radiotracer doses.[131,132] This is particularly beneficial for patients with cardiac amyloidosis or cardiac sarcoidosis who experience orthopnea leading to difficulties in lying in supine position for a long time. In other words, shorter scan times would considerably alleviate discomfort. Moreover, lower radiotracer doses and reduction in CT radiation may enable more regular PET scans for follow-up or screening purposes. Finally, LAFOV scanners allow for simultaneous dynamic imaging of all affected organs. The use of kinetic modelling has the potential to enhance the assessment of therapy response and differentiate between different types of amyloidosis, although this approach has not been extensively studied.[133-135]

Infective Endocarditis

Infective endocarditis is the colonization by pathogens of the inner lining (endothelium) of the heart or intracardially implanted materials, such as prosthetic valves.[136] Formerly, echocardiography was the primary imaging technique used to diagnose infective endocarditis by depicting vegetations.[137] However, since 2015 multimodality imaging has been introduced to improve diagnostic yield, especially when prosthetic material is present.

[^{18}F]FDG PET/CT can detect disseminated infectious disease in patients with and without clinical evidence for extracardiac localizations.[137] Furthermore, in case of prosthetic valves, adding [^{18}F]FDG PET/CT, next to echocardiography, as a major diagnosis criterion improved the diagnostic sensitivity to >90%.[138,139] This improvement has not been observed in the case of native valves, where the infection is usually localized on the tip of the native valve, and results in larger motion artefacts on the scan. However, with the use of gated imaging, this artefacts can potentially be reduced, improving the interpretability of [^{18}F]FDG PET/CT.[140]

In general, motion correction leads to the loss of signal-to-noise ratio, necessitating increased acquisition time.[140] With the improved sensitivity of LAFOV scanners and the introduction of e.g. CardioFreeze^{TM}, the acquisition time can be reduced again, concurrently allowing for full body assessment of disseminated infectious diseases.[140,141] Furthermore, the use of LAFOV dynamic imaging will potentially improve differentiation between physiological and pathophysiological uptake of [^{18}F]FDG PET/CT, potentially improving the sensitivity of [^{18}F]FDG PET/CT for infective endocarditis and dissemination even further.[142-144]

The Critically Ill Patient

The most critically ill patients, including those with severe endocarditis, necessitate admission to the Intensive Care Unit (ICU) for invasive mechanical ventilation, hemodynamic support, and renal replacement therapy.[145] Of these patients, a large number exhibit extra-cardiac involvement, mainly localized in the central nervous system, spleen, bone, joints and kidneys.[146]

The use of [^{18}F]FDG PET/CT in critically ill patients is uncommon.[147,148] Only a limited number of small studies have been performed in this patient category, all reporting good sensitivity of [^{18}F]FDG PET/CT for assessing infection

foci.[149-152] Routine use of [^{18}F]FDG PET/CT in critically ill patients has been limited due to the intensive continuous organ support, hampering in-house transportation. To mitigate risk during transportation the time spent outside the ICU should be minimized.[153,154] This is enabled with the introduction of LAFOV scanners, approaching scanning times of regular CT scans. Furthermore, limiting staff radiation exposure is challenging since these patients require constant monitoring and frequent care. The feasible dose reduction using LAFOV systems will allow a reduction of staff radiation exposure. Together with the implementation of a strict scanning protocol, [^{18}F]FDG PET/CT could become accessible for routine use in critically ill patients.[147,155,156]

Discussion and Future Perspectives

The introduction of LAFOV PET/CT systems represents a breakthrough in technological advancement within the field of medical imaging. It also offers a wide range of opportunities for the study and better understanding of various pathologies. In the specific case of CVDs, previous studies have already extensively depicted the different areas of opportunity, mainly regarding the possibility of studying in real time the crosstalk between the heart and other organs/systems. However, it is necessary to understand both the technical opportunities and the challenges that LAFOV scanners face in order to reach the full potential of this kind of system and critically evaluate the installation of these systems in more healthcare centres.

The implementation of LAFOV scanners relies, firstly, on the availability of multiple resources regarding clinical infrastructure, such as the physical space for the scanner itself, other adjacent rooms for patients and data storage/processing, but also virtual space, software capacity, and robust IT-solutions, as the data volumes that are produced are extremely large. Secondly, it is highly recommended to have an on-site cyclotron, as the most promising radiotracer for multiorgan evaluation of CVD is [^{15}O]H_2O, a radiotracer that is only available by producing it on-site. Moreover, a logical new application of LAFOV PET in CVD (e.g. atherosclerosis) would be dual-radiotracer imaging for the simultaneous evaluation of perfusion and function by using a flow tracer (ideally [^{15}O]H_2O) in combination with a different radiotracer (e.g. [^{18}F]NaF). Finally, it is important to realize the other issues related to image processing of LAFOV data, such as the presence of motion and attenuation artefacts that remain without a standardized solution in terms of a TB approach. Currently, the best way to overcome these pitfalls is the simultaneous implementation of different tools developed in organ-specific SAFOV protocols. Software packages for processing images from LAFOV PET scanners are limited, particular in the CVD field.

Nevertheless, efforts are being made by vendors and various research groups to offer technical solutions for the aforementioned challenges. Significant advances have been made in the development of pipelines and software for IDIF/PBIF determination, motion artefact detection and correction, and organ segmentation. Moreover, parallel efforts for the reduction of the CT radiation dose have been performed using distinct methodologies. The improved statistics regarding sensitivity, combined with the opportunity for dose and scan time reduction, makes LAFOV PET an attractive device to explore the role of this modality in pathological states, where the use of PET/CT remains unexplored (i.e. amyloidosis, sarcoidosis), or where the use of minimal-length imaging studies becomes crucial (i.e. critically ill patient). Finally, the calculation and validation of clinically relevant quantitative metrics in CVD, other than MBF, seems reachable in the short-term only with the use of LAFOV devices, as these devices exclusively allow for simultaneous multiorgan kinetic fitting, particularly relevant to quantify disease burden in CVD with multiorgan involvement (e.g. atherosclerosis) or systemic diseases with cardiac involvement (e.g. amyloidosis). Finally, TB PET may provide unique insights into the effects of novel cardiovascular therapies that exploit systems interaction and the biology of the body as a whole.

Conclusion

The use of LAFOV PET/CT devices promises to enhance the study of CVD by enabling the construction of high-quality static images and the capacity to perform quantitative dynamic imaging of the entire cardiovascular system simultaneously. Despite several advantages, LAFOV PET/CT in CVD still faces several technical challenges that must be adequately addressed and overcome to ensure reproducible results and to introduce this modality for the routine cardiovascular evaluation of patients.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Riemer H. J. A. Slart reports a relationship with Siemens Healthineers that includes: funding grants. Riemer H. J. A. Slart reports a relationship with Pfizer that includes: funding grants. Andor W. J. M. Glaudemans reports a relationship with Siemens Healthineers that includes: funding grants. Charalampos Tsoumpas reports a relationship with Siemens Healthineers that includes: funding grants. Charalampos Tsoumpas reports a relationship with Positrigo that includes: funding grants. Charalampos Tsoumpas reports a relationship with General Electric Healthcare that includes: funding grants. Charalampos Tsoumpas reports a relationship with Positrigo that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

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