Role of FDG-PET/CT in the evaluation of infectious and inflammatory disease

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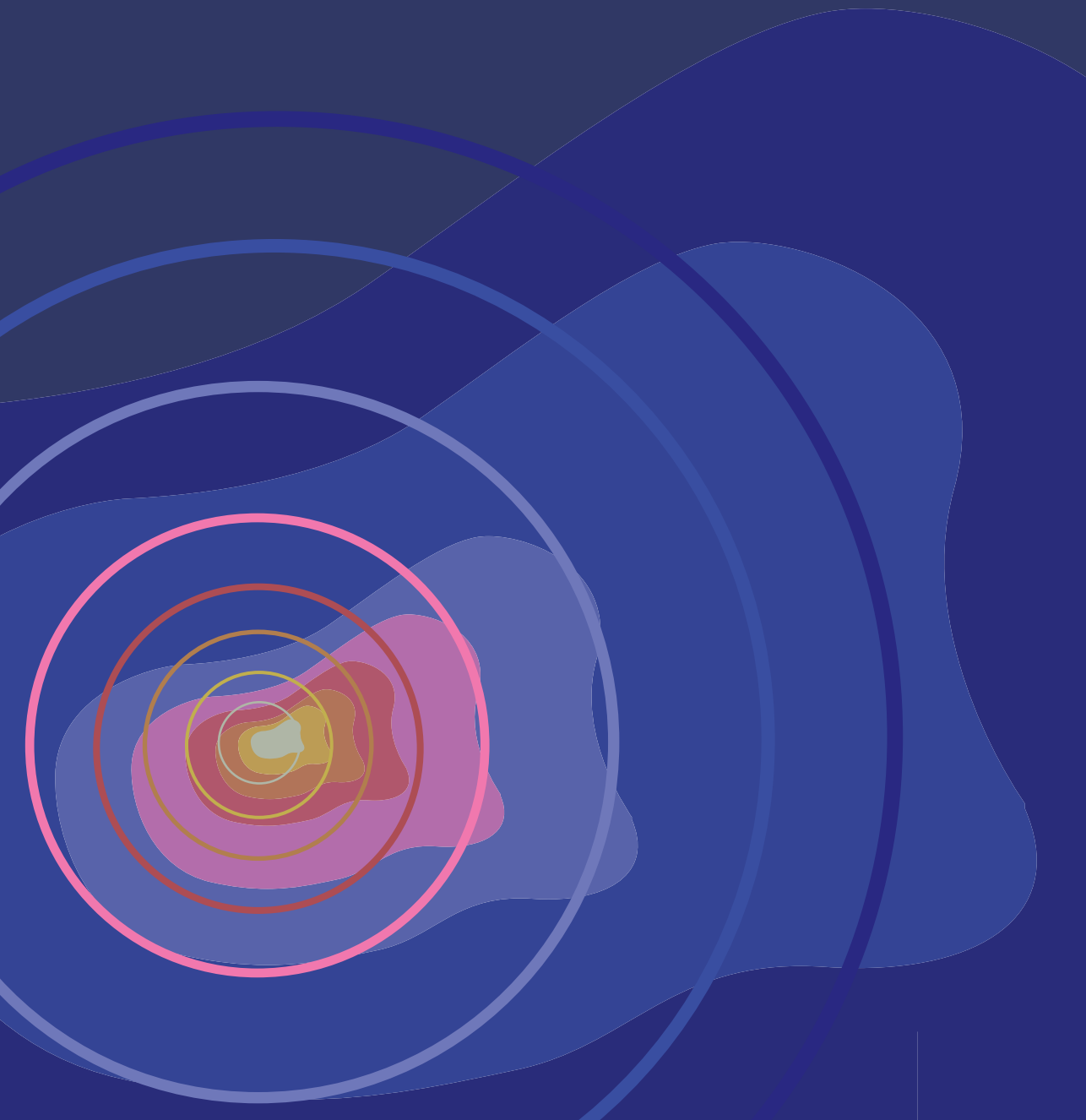
CHAPTER 1

General introduction



DIAGNOSING INFECTIOUS AND INFLAMMATORY DISEASE

'Infectious and inflammatory disease' covers a large umbrella of different diseases. Historically, infectious disease, especially contagious disease, has always been the leading cause of death worldwide[1]. After the development of vaccines, sewage systems, antibiotics, and an increase in knowledge about the spread of infectious disease, most deaths in developed countries can nowadays be attributed to heart disease and cancer[2]. Nevertheless, infectious and inflammatory disease remains an important cause of morbidity and mortality in developed countries, and persists as the leading cause of mortality in some developing countries[3].

After a steep decline in the 20th century, the morbidity and mortality of infectious disease in developed countries is projected to rise again in the coming years[4]. Various factors can be identified for this increasing trend. First, due to an ageing population, more and more people require invasive procedures such as hip replacements, artificial valve replacements, implantable cardioverter-defibrillators, vascular grafts, et cetera. Implantation of foreign materials into the body poses an increased risk of dangerous and difficult-to-treat infections, not only shortly after surgery, but also decades after implantation[5]. Sometimes, the only curative option is to remove the infected materials. However, this is not always possible due to patient comorbidity. Second, due to widespread use of antibiotics, antimicrobial resistance is rising, especially in countries where antibiotics can be bought over-the-counter. When infections are caused by highly resistant bacteria, it can be very difficult to treat the infection, leading to increased mortality[4]. Third, more and more people are immunocompromised mostly due to increased use of immunosuppressive medication, for example after solid organ transplantation[6]. This is also associated with an increased risk of mortality due to infection.

Treatment of infectious and inflammatory disease usually starts with establishing the correct diagnosis. The most common infections, such as pneumonia or a urinary tract infection, can usually be diagnosed relatively easily based on symptoms, clinical examination, and plain diagnostics such as an X-ray, ultrasonography or urinalysis. Sometimes, however, patients may feel ill and present with elevated inflammatory markers while the disease causing these symptoms cannot be established based on history-taking, physical examination, and conventional diagnostics. In these cases, targeted imaging with more advanced techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) are often used to identify the source of infection or inflammation. However, these techniques can only be used to detect anatomic abnormalities[7]. Especially in low-grade infections or infected foreign materials, anatomic abnormalities, such as abscesses, may not be present or only develop at a later stage[8]. In addition, in patients with bacteremia of unknown origin, it is not only important to locate the origin of the infection for adequate source control, but also to detect disseminated infection foci when patients remain ill while being treated adequately[9]. This requires sensitive full-body imaging, for which CT and MRI are less frequently used. In patients with implanted foreign materials such as artificial valves or hip replacements, explantation of the foreign material may be the only way to cure the infection. As this requires invasive

surgery, it is extremely important to establish the correct diagnosis before reperforming surgery, or administering antibiotics for long periods of time[10]. Furthermore, in patients suspected of inflammatory diseases such as vasculitis, being able to assess metabolic activity of blood vessels may prevent unnecessary invasive exams such as (multiple) biopsies before a final diagnosis is established[11]. These are just some examples where FDG-PET/CT can play a very valuable role, and has shown promising results in various settings[9].

FDG-PET/CT

Basic principles of PET

Positron Emission Tomography (PET) is a nuclear imaging technique of increasing interest in the imaging of infectious and inflammatory disease[12]. The technique exploits the properties of positrons (β+), which are essentially the antimatter of electrons (e-). Stable atoms do not eject positrons. When atoms are unstable because they contain too many protons, which are positively charged, relative to neutrons, which are neutral, the atom can eject a positron to turn a proton into an additional neutron, resulting in a (more) stable nucleus. This process is also called β+ (positron) decay[13].

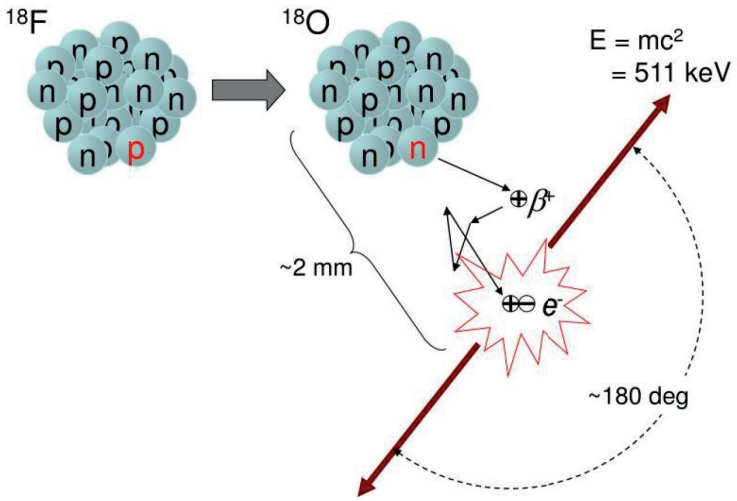


***Figure 1** | Graphic example of β+ decay[14]*

The ejected β+ then collides with its antiparticle e- in the electron shell of the atom, causing electron-positron annihilation and the release of two anti-collinear high-energy photons (**Figure 1**)[15].

These high-energy photons can be detected by PET-scanners (**Figure 2**). The inner side of a PET camera consists of scintillator crystals, for example bismuth germanate or lutetium oxyorthosilicate[16]. This is a special material that shortly emits visible or ultraviolet light when hit by high-energy photons. This light is then detected by an outer photosensor. Based on which sensors are triggered at the same time, the location of the electron-positron annihilation can be calculated for image reconstruction. Other factors such as attenuation correction and time of flight are also accounted for in modern-day PET/CT machines.

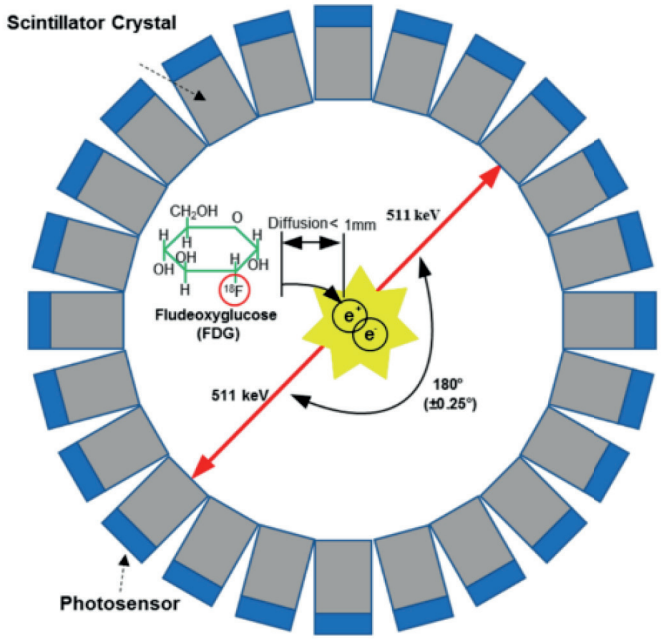


Figure 2 | *Basic display of PET-scanner components*[17]

To image tissues with PET, radiopharmaceuticals that emit positrons have to be administered to patients. These radioisotopes can be used to label molecules of interest, based on the type of examination physicians want to perform. One of the most commonly used radioisotopes is ^{18}F, an unstable isotope of fluorine with a half-time of 110 minutes[18]. In infectious disease, inflammatory disease, and oncology, ^{18}F is often labeled to an analogue of glucose to create 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG). When using this tracer, PET can be used to visualize in which tissues much glucose is being consumed.

FDG-PET/CT can be used to evaluate the whole body for a suspected infection or inflammatory focus within one examination. White blood cells and other inflammatory cells have a high glucose metabolism compared to other cells. Glucose transporters are also upregulated by other inflammatory mediators, such as cytokines. Because white blood cells and other inflammatory mediators are drawn to sites of infection and inflammation, these sites are often readily visible on FDG-PET/CT, even before gross anatomical changes, such as abscess formation, have occurred[19]. In the last two decades, FDG-PET/CT has shown its value in more and more infectious, inflammatory, and autoimmune diseases[9]. Because PET imaging has gained more and more interest after the recent development of hybrid PET/CT camera systems, and the main focus of FDG-PET/CT imaging was on oncology, the potential benefits of FDG-PET/CT in infectious and inflammatory diseases have been poorly studied in some diseases, mostly due to small sample sizes[20]. This is especially true for certain specific patient populations, such as children or intensive care patients.
FDG-PET/CT can also present several challenges with regards to patient preparation and organ-specific limitations that need to be taken into account as well. Additionally, it can be challenging to select those patients who would benefit most from undergoing FDG-PET/CT examination, and which patients are less suitable for this diagnostic technique.

SCOPE AND OUTLINE OF THIS THESIS

In this thesis, the use of FDG-PET/CT in several infectious and inflammatory diseases and patient populations will be investigated. **Chapter 2** presents an extensive overview of infectious diseases for which FDG-PET/CT is currently used in clinical practice, which also serves as a more elaborate introduction for the remainder of the thesis. Alternative nuclear imaging techniques and potential future applications are discussed as well. **Chapter 3** presents various factors that affect the diagnostic yield of FDG-PET/CT in patients with bloodstream infection. For example, the influence of administering antibiotic treatment before performing FDG-PET/CT is investigated, amongst other factors. **Chapter** 4 presents the use of FDG-PET/CT in patients with autosomal dominant polycystic kidney disease who are suspected of a cyst infection. The clinical consequences of FDG-PET/CT on their treatment are analyzed as well. Thereafter, **Chapter 5** displays a pictorial essay of five interesting patients with autosomal dominant polycystic kidney disease, who underwent FDG-PET/CT to identify their focus of infection. **Chapter 6** presents three interesting cases of patients with Lemierre's syndrome, a rare syndrome involving infectious thrombophlebitis of the internal jugular veins, where FDG-PET/CT proved helpful. In **Chapter 7**, the use of FDG-PET/CT in intensive care patients with bloodstream infection is discussed. The influence of PET imaging quality on its sensitivity and specificity are highlighted as well, including reasons for decreased image quality and practical bottlenecks of performing FDG-PET/CT in patients admitted to the intensive care. **Chapter 8** describes the clinical implications and potential causes of increased FDG avidity of the bone marrow and spleen in patients with bacteremia, as this phenomenon is sometimes seen in patients with infectious or inflammatory disease without a clear explanation.

Chapter 9 highlights the use of FDG-PET/CT in children with fever of unknown origin. The outcomes of performing FDG-PET/CT in this specific population are discussed, which include many different infectious, inflammatory, and malignant diseases. Factors associated with detecting the source of fever on FDG-PET/CT are analyzed as well. **Chapter 10** focuses on performing FDG-PET/CT in patients with bacteremia of unknown origin, who were hyperglycemic before the procedure. This can influence the FDG avidity of infection foci due to direct competition at cellular glucose transporters. The sensitivity and specificity at various glucose levels are discussed, along with practical solutions for glucose management prior to FDG-PET/CT. **Chapter 11** presents a literature review on the limitations and pitfalls of FDG-PET/CT in infection and inflammation imaging, also highlighting other nuclear imaging techniques and future developments of FDG-PET/CT to overcome these challenges. **Chapter 12** provides the summary of this thesis, along with a general discussion, conclusion, and future applications of FDG-PET/CT for the evaluation of infectious and inflammatory disease.

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