Introduction
Chapter 1. Introduction

1.1 Positron emission tomography

Positron emission tomography (PET) is a medical imaging technique capable of measuring a wide range of (patho)physiological processes in vivo. Apart from its diagnostic purposes in, for instance, assessing the presence of metastases in cancer, and diagnosing Alzheimer’s disease or ischemic heart disease, PET can be used for monitoring response to treatment and is increasingly being used in the development of new drugs.

PET makes use of ‘radiopharmaceuticals’ or ‘radiotracers’: biological molecules labeled with unstable, positron emitting nuclei such as $^{11}$C, $^{13}$N, $^{15}$O and $^{18}$F. A tracer amount (pico- to nanomoles, i.e. amounts that are assumed to have no biological effects) of such a molecule is injected into a subject, after which it distributes throughout the body. This distribution can be measured over time and the observed time course can be used to quantify tissue function using pharmacokinetic models (1). A wide range of tissue functions, such as blood flow, glucose consumption, neuroinflammation and hypoxia, can be measured depending on the radiotracer being used.

The positron emitting nucleus attached to the radiotracer is unstable and will decay by emitting a positron, the antiparticle of an electron. This positron will travel a short distance (within tissue at most a few millimeter (2)), during which it will collide with electrons in the surrounding tissue, ultimately combining with an electron. This combination of positron and electron is very unstable and will almost immediately annihilate, resulting in two photons, each with a fixed energy $E$ of 511 keV. This fixed energy relates to the mass $m$ of the annihilated particles (electron and positron) according to the well known relationship (3)

$$E = m \cdot c^2$$

in which $c$ is the speed of light. The annihilation photons travel in approximately opposite directions and can be measured by the ring of detectors in a PET scanner. When two detectors are triggered almost simultaneously, i.e. within a certain coincidence time window of several nanoseconds, the line of response (LOR, Figure 1.1a) along which the original annihilation event took place is known. When the scan is complete, all data (typically millions of coincidences) are used to reconstruct images reflecting the radioactivity distribution within a scan.

Unfortunately, not all measured coincidences are ‘true’ coincidences (4). For instance, a photon may interact with tissue in the patient, lose some of its energy and continue its path under a different angle (Compton scatter, Figure 1.1b). This may result in incorrect placement of the LOR and data must be corrected for this effect. This can be performed in multiple ways, such as by excluding photons with low energy and by simulating the scatter distribution, based on measured activity and anatomical properties of the subject, and subtracting this simulated distribution from the reconstructed data.

Another type of ‘false’ coincidences is caused by random events (Figure 1.1c), when by chance two (or more, a multiple event) photons that do not originate
1.1. Positron emission tomography

from the same positron annihilation are measured simultaneously, again resulting in an incorrect LOR. This effect is especially pronounced at very high count rates as observed shortly after injection. A correction for this phenomenon is performed using a delayed coincidence window, in which only random events occur. The rate of random coincidences is assumed to be equal in the normal and delayed coincidence windows and, therefore, delayed coincidences can be subtracted from the normal coincidences yielding random-free data.

Finally, since photons originate from within the patient, some of them are absorbed ('attenuated') in tissue before reaching the detectors. Since PET depends on simultaneous detection of a pair of photons, attenuation is independent on the location along the line of response where the annihilation event took place. Therefore, for each line of response, exact correction factors can be derived from a transmission scan, which measures attenuation of an external radiation source. These transmission scans can be performed using rotating positron emitting sources or, in case of a PET/CT scanner, using a CT scan. Combining attenuation correction with corrections for random and scattered events mentioned above yields quantitative data of radioactivity concentrations, enabling absolute quantification of tissue functions using PET.

On state-of-the-art PET/CT scanners, detectors and electronics are fast enough (time resolution of 600 ps) to measure a difference in arrival time between both photons originating from a single annihilation event (6). This so-called time of flight (TF) information can be incorporated in the reconstruction, so that annihilation events are not only assigned to an LOR, but to a specific part on that LOR (Figure 1.1d). This technique has led to an increased signal to noise ratio.
1.2 Cardiac PET

Since the biologically highly important atoms carbon, nitrogen, oxygen and fluorine each have isotopes that can be used for PET, a wide range of radiotracers is available. In addition, the number of radiotracers and hence the number of applications is increasing rapidly. Examples of clinical or research applications in cardiac PET are measurements of myocardial blood flow (MBF), metabolism and sympathetic innervation. Work presented in this thesis focuses on these applications and therefore, they are briefly described below, along with several examples of radiotracers used.

1.2.1 Blood flow

The main clinical application of cardiac PET is the assessment of regional MBF in patients with known or suspected coronary artery disease (CAD) (7,8), using $^{13}\text{N}$NH$_3$ (9), $^{15}\text{O}$H$_2$O (10–14) or $^{82}\text{Rb}$ (15, 16). Each of these tracers has a short half-life, enabling stress-rest protocols in a single scanning session but forces tracer production to be in close proximity to the PET center. Advantages and disadvantages of each tracer are given in more detail in Chapter 2. In addition to the aforementioned tracers, a new and promising $^{18}\text{F}$-tracer is under development (17). This tracer does not require on-site tracer production and can be distributed regionally, enabling wide-spread application, and is reported to produce images of excellent quality (18). However, its long half-life may make stress-rest protocols more complicated and more clinical experience with this new tracer is required.

Since the introduction of PET/CT scanners, MBF measurements with PET have gained renewed interest, as assessment of MBF can be combined with anatomical imaging of calcifications of coronary arteries, using CT, in a single scanning session. This yields powerful complementary diagnostic information, showing not only presence and location of calcifications, but also functional effects i.e. whether calcification results in reduced MBF or even scar formation. This is important since non-significant CAD (without significant reductions in MBF) as based on invasive angiographic findings requires a different treatment strategy compared to significant CAD (with significant reductions in MBF): Percutaneous coronary intervention (PCI, opening of narrowed coronary arteries using a balloon catheter) confers no symptomatic benefit for patients with non-significant CAD and is, in fact, associated with a worse prognosis for these patients (19). In contrast, therapy consisting of PCI and medical therapy is superior compared to medical therapy alone for patients with significant CAD (20).

Clearly, functional information is required in addition to anatomical information to differentiate between significant and non-significant CAD and ideally, this is performed before patients are referred for invasive angiography. A combination of MBF imaging using PET and CT angiography has been shown to be able to differentiate between significant and non-significant CAD with excellent diagnostic accuracy (21, 22). Considering the prevalence of significant of CAD
in these studies, which was 41%, PET and CT could be used as a gatekeeper for invasive angiography, filtering out over half of the patients all of which do not need to undergo invasive angiography. Figure 1.2 shows an example where a significant reduction in MBF (Figure 1.2a) but no scar formation (Figure 1.2b) is observed in the presence of a large stenosis (Figure 1.2c). During invasive measurements (Figure 1.2d), this plaque was considered clinically significant, confirming PET and CT findings.

In several studies, it has been shown that MBF imaging using PET not only has higher diagnostic accuracy compared to SPECT (7), a different modality used for MBF imaging, but that it is also more cost effective (23) and both image
quality (24) and reader certainty are improved (25). Diagnostic accuracy of absolute quantification of MBF using PET is higher as compared to qualitative MBF imaging (26). The main advantage of quantitative over qualitative MBF imaging lies in the ability to diagnose patients with triple vessel disease or balanced CAD. Qualitative MBF imaging relies on the presence of a region with preserved MBF which may be absent in these patients. This results in a failure in uncovering the entire disease or only select regions supplied by arteries with the most severe stenoses are uncovered (27). Quantification of MBF can also be used to exclude ischemia in symptomatic patients when heterogeneous but sufficiently high MBF values are found (8). Furthermore, quantitative MBF values can be used to calculate coronary flow reserve (defined as the ratio of stress and rest MBF) which may be of great clinical importance (27–32).

1.2.2 Metabolism

Imaging of various metabolic processes may be of interest for both clinical and research purposes and different PET radiotracers are available for different metabolic processes such as glucose metabolism, oxidative metabolism and, to a lesser extent, fatty acid metabolism (see (33) for a complete overview). The glucose analogue [18F]FDG (34), a marker of glucose metabolism, is the most commonly used radiotracer and is often used for clinical assessment of myocardial viability. Viable but dysfunctional myocardium increases its glucose utilization, at the expense of fatty acids utilization, as substrate for its energy production (35), an adaptive response to mild but chronic ischemia due to reduced MBF. This increase in glucose utilization can be measured using [18F]FDG and myocardial regions with reduced MBF but preserved glucose metabolism (‘mismatch’) are expected to regain function when MBF is be restored by treatment (36, 37). In contrast, regions with reduced MBF and reduced [18F]FDG uptake will not regain contractile function after treatment and are likely necrotic or scar tissue. Presence of mismatch was a strong predictor of prognosis and improvement of symptoms for patients with chronic ischemia undergoing revascularization (38–40) and could potentially be used for patient selection prior to revascularization.

In contrast to [18F]FDG, [11C]acetate (41) is generally used in a research setting. After it is taken up into the myocardium, [11C]acetate is a specific marker for myocardial oxidative metabolism (42), irrespective of whether the myocardium utilizes fatty acids or glucose. [11C]acetate is rapidly taken up, with uptake rates that are proportional to blood flow (43). Then, [11C]acetate is oxidized in the citric acid cycle and [11C]CO2 is formed, which is excreted from the tissue. The rate of excretion is a measure of oxygen use, which is required for both glucose and fatty acid metabolism. Similarly as for glucose consumption measured with [18F]FDG, preserved oxygen consumption as measured with [11C]acetate was found to be necessary for functional recovery (44) and capable of identifying patients likely to benefit from revascularization (45). In addition, oxygen consumption can be used to calculate myocardial efficiency by relating it to the amount of work performed by the myocardium. In various heart con-
ditions, coupling between oxygen use and myocardial work is lost (46,47) and more oxygen is required to preserve normal cardiac function (i.e. a reduced myocardial efficiency). Counteracting this reduction in efficiency is an important therapeutic target and therefore, myocardial efficiency as measured using $[^{11}\text{C}]$acetate can be used to monitor treatment, such as in (48–50).

1.2.3 Sympathetic innervation

Since the sympathetic nervous system plays a key role in cardiac stimulation and impulse propagation, several radiotracers have been developed to assess processes of this system. Examples of radiotracers are $[^{18}\text{F}]$fluorodopamine (DOPA) (51) and $[^{11}\text{C}]$epinephrine (EPI) (52), both true catecholamines, and $[^{11}\text{C}]$hydroxyephedrine (HED) (53) and $[^{11}\text{C}]$phenylephrine (PHEN) (54), both catecholamine analogues (for a complete list see (55)). Under normal circumstances, sympathetic activity in the left ventricle is homogeneous, but defects, regions with low or even no sympathetic activity, are encountered often in ischemic heart disease (56–58) or in idiopathic dilated cardiomyopathy (59). In addition, innervation may be hampered in the entire left ventricle in a subset of patients with heart failure (59). These disturbances in innervation may lead to arrhythmias and sudden cardiac death and are important for prognosis in these patients or to determine which patients need anti-arrhythmic drugs or an implantable cardioverter-defibrillator for primary prevention (58,60–63).

1.3 Tracer kinetic modeling in cardiac PET

1.3.1 Scanning protocol

For absolute quantification of cardiac PET studies, a dynamic PET scan, i.e. a scan measuring radiotracer distribution over time, is required. This scan is started simultaneously with the bolus injection of a radiotracer. After completion of the scan, acquired data are reconstructed in several frames, each of which represents radiotracer distribution at a given time point. For accurate measurements of the first pass of the bolus through the heart, which is essential for reliable modeling, the first frames are typically very short (5-10 s). In contrast, later frames can be longer based on the smaller changes in activity concentrations at later times. These longer frames at later times also compensate for the reduction in count rate due to radioactive decay of the tracer.

In cardiology, scan durations can vary widely. For MBF, radiotracers with rapid kinetics are of interest. When a radiotracer has rapid kinetics, isotopes with short half-lives can be used and this enables two MBF scans, one during resting conditions and one during stress, to be performed in a single scanning session. On the other hand, radiotracers used for quantification of metabolic processes and innervation have slower kinetics, requiring longer scanning times (40-60 minutes). As a consequence, isotopes with longer half-lives must be used.
Chapter 1. Introduction

Figure 1.3. Example of images of $^{15}$O$\text{H}_2$O uptake between 1 and 6 minutes post injection (A) and of absolute MBF calculated after kinetic analysis (B), derived from the same scan. As can be seen, kinetic analysis is essential for analysis of $^{15}$O$\text{H}_2$O scans.

1.3.2 Input functions

In order to obtain quantitative results, it is necessary to measure the supply of the radiotracer to tissue (i.e. arterial whole blood or plasma concentrations) as function of time. This so-called arterial plasma input function can be measured invasively using an on-line blood sampler and arterial cannulation. During the scan, blood is continuously withdrawn from the radial artery of the patient and measured externally, resulting in a blood sampler input function (BSIF). Whilst BSIF is considered the gold standard for measuring the arterial plasma input function, its invasiveness has limited use of BSIF to research studies. Since the largest artery, the aorta, is in the field of view of myocardial PET studies, an attractive alternative is to obtain blood concentrations directly from the PET scan itself. In this way an image derived input function (IDIF) is obtained and online blood sampling (i.e. arterial cannulation) can be omitted. Feasibility of IDIF, however, is dependent on accurate corrections for scattered and random events and requires validation for each scanner and tracer before it can be considered as an alternative for online blood sampling.

For most radiotracers, an additional step is needed to derive the arterial plasma input function. These radiotracers are partially bound in the blood, or radiolabeled metabolites are formed in the tissue and enter the plasma. Only radiotracer molecules not bound in the blood can be taken up by tissue and a correction factor has to be applied for the ratio of radiotracer in plasma and in (whole) blood. In addition, radioactive metabolites may not enter the tissue and, therefore, the input function has to be corrected for the fraction of metabolites in plasma. At set times during the scan, continuous blood sampling is interrupted and manual samples are taken and analyzed for plasma-to-blood ratios and plasma metabolite fractions. When no continuous blood sampling is performed, manual samples might be taken from the (venous) infusion line instead, although this requires validation for each tracer since venous and arterial values can differ significantly (64). Using metabolite and plasma data, the final metabolite corrected plasma input function can be obtained. Note, however that for $^{15}$O$\text{H}_2$O and $^{82}$Rb, this step is not necessary due to the lack of significant metabolism during the scan.
1.3.3 Radiotracer kinetic analysis

For several radiotracers, the most obvious example being $^{15}$O$\text{H}_2\text{O}$, routine radiotracer kinetic analysis is required in order to measure tissue function (Figure 1.3) as no simplified measures are available. In general, kinetic analysis of dynamic PET data is based on the use of compartment models (Figure 1.4). In these models, each compartment represents a volume (i.e. blood or tissue) or chemical state (i.e. bound or free radiotracer) in which the radiotracer is rapidly distributed. Exchange between compartments is described by rate constants ($K_1$, $k_2$, $k_3$ and $k_4$ in Figure 1.4) and these constants can be derived when both input function (i.e. plasma concentrations, $C_P(t)$) and tissue concentrations ($C_T(t)$ as a function of time) are known.

Reversible single tissue compartment model

The simplest model in Figure 1.4 is the reversible single tissue compartment model (Figure 1.4a), which is used for quantification of $^{15}$O$\text{H}_2\text{O}$, $^{82}$Rb and $^{[11]}\text{C}$acetate kinetics. It consists only of an input function ($C_P(t)$) and a single tissue compartment ($C_T(t)$). The rate constants in this model are $K_1$ (mL·g$^{-1}$·min$^{-1}$) and $k_2$ (min$^{-1}$), representing the rate of influx of radiotracer from plasma into tissue and the rate of clearance of radiotracer from tissue, respectively. For this model, the total volume of distribution ($V_T$, (mL·g$^{-1}$)) is used as a measure of radiotracer uptake. $V_T$ is not a physical volume; instead it represents the ratio of concentrations in tissue and in plasma during equilibrium. In other words: a high $V_T$ means that net radiotracer uptake in tissue is high. Since equilibrium is rarely accomplished during a PET scan, it can be calculated as the ratio of $K_1$ and $k_2$.

Irreversible two-tissue model

For radiotracers that are metabolically trapped in tissue (such as $^{[13]}\text{N}$NH3 or $^{[18]}\text{F}$FDG) or bind to a receptor or vesicle (such as $^{[11]}\text{C}$HED), the reversible single tissue model might be insufficient to describe their kinetics. For this, both the irreversible (Figure 1.4b) and reversible (Figure 1.4c) two tissue compartment model can be used. The irreversible two tissue compartment model adds a compartment with a third rate constant $k_3$ (min$^{-1}$) that represents unidirectional trapping or binding of the radiotracer in this second compartment.
In this model, free and non-specifically bound radiotracer in the first compartment (non-displaceable) can not only be cleared from the tissue, but can also be metabolized or bound to a receptor/vesicle within the tissue compartment. It is important to note that this second compartment is not a physical compartment, but a chemical compartment as trapped and free radiotracer are often in the same physical volume (i.e. within the tissue). For this model, $V_T$ is an inappropriate measure and $K_i$, the net rate of influx is used. $K_i$ ($\text{mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$) is defined as the influx rate $K_1$ multiplied by the fraction of radiotracer in the free compartment that is trapped (i.e. $k_3/(k_2+k_3)$).

**Reversible two-tissue model**

The final model in general use is an extension of the irreversible two tissue compartment model, the reversible two tissue compartment model (Figure 1.4c). In contrast to the irreversible model, this reversible model assumes that bound radiotracer can dissociate within the time of the study. To represent this process, $k_4$ ($\text{min}^{-1}$) is added to the model, the rate constant representing dissociation of the radiotracer.

Similarly to the reversible one tissue compartment model, it is possible to derive volumes of distribution for each compartment (i.e. the volume occupied by the radiotracer in a compartment during equilibrium relative to the total tissue volume). For the non-displaceable compartment, $V_{NS}$ is defined as $K_1/k_2$ whilst for the specific compartment, $V_S$ is defined as $(K_1/k_2)(k_3/k_4)$. The total volume of distribution ($V_T$) can then be calculated as the sum of $V_{NS}$ and $V_S$. Finally, for receptor studies, the binding potential ($\text{BP}_{ND} = k_3/k_4$, dimensionless) is used which represents a combination of the total number of receptors and the affinity of the radiotracer for that receptor. The affinity is assumed to be (relatively) constant for a radiotracer and, if this assumption is valid, changes in $\text{BP}_{ND}$ directly represent changes or differences in receptor density.

**Simplified methods**

For some radiotracers, such as $[11\text{C}]$acetate, $[11\text{C}]$HED and $[18\text{F}]$FDG, simplified analytical methods are in use, although not all of these have been validated using full kinetic analyses. For radiotracers with specific uptake, late radioactivity concentrations can be normalized to either the injected dose per patient weight, yielding standardized uptake value (SUV), or to the total amount of activity in the blood during a scan, yielding the so-called retention index (RI). For acetate, often $K_{\text{mono}}$ is used as an alternative to $k_2$. In this case, the downslope of the tissue curve is fitted, eliminating the need for an accurate input function. Finally, other simplified methods, such as reference tissue models, are available, but they have been developed specifically for brain studies and are not discussed here.
1.4 Recent improvements in cardiac PET

Introduction of 3D scanners (Figure 1.5), which have become increasingly available in recent years, has led to an improvement in sensitivity (65) and this can be used to improve image quality and/or reduce dose to the patient. In dynamic PET studies using isotopes with short half-lives, this increased sensitivity is especially important. The scanner must be capable of accurately handling high count rates shortly after injection (when all injected activity is within a small region within the field of view), whilst it must be sensitive enough to provide accurate measurements after the radioactivity has decayed and spread through-

**Figure 1.5.** Schematic representation of the differences between 2D (A) and 3D (B) data acquisition. In 2D mode, septa (gray lines) between detectors (black rectangles) block oblique coincidences, whilst in 3D mode, both oblique and non-oblique coincidences are measured. This leads to increased sensitivity, but comes at the cost of an increase in scatter fraction and random coincidences.

**Determination of optimal model**

In general, adding more parameters to a model increases goodness of fits. Increasing the number of parameters, however, also makes results more sensitive to noise, resulting in reduced precision of fitted parameters. For each radiotracer, the optimal model has to be defined based on radiotracer kinetics, accuracy of fits and parameter stability. When data on test-retest variability is available, this should be included in determining the optimal model. In addition, it is possible that rate of exchange between two distinct compartments is so fast that they cannot be separated from each other kinetically. In that case, a model that should have two tissue compartments based on biological behavior, can only be fitted to a single tissue compartment model. Finally, for each radiotracer, potential use of an IDIF needs to be validated by comparing results with those using full arterial sampling. This is because partial volume and spill-over effects, and possible inaccuracies in e.g. scatter correction will have different impact on the kinetic analyses of different tracers.
out the entire body. Use of new, faster detector crystals (build from lutetium oxyorthosilicate (LSO) or lutetiumyttrium oxyorthosilicate (LYSO)) has further improved the sensitivity (66). In addition, these detector crystals have enabled introduction of TF PET, as described above. Finally, merging PET and CT systems has enabled fast and precise attenuation correction (<1 min); with a reduced risk of patient motion between PET and attenuation scans, or during the attenuation scan. These developments have greatly improved scanning statistics and consequently image quality of state-of the-art PET/CT scanners.

Shortly after the introduction of 3D scanners, new (iterative) reconstruction algorithms have become widely available (67). These iterative reconstructions are less sensitive to noise compared with numerical reconstructions (i.e. the gold standard for reconstructions, filtered back-projection) and can include specific scanner information in the reconstruction. However, a careful assessment of the reconstruction settings is essential as iterative reconstructions can introduce a bias when incorrect settings are used which can ultimately result in different results obtained after kinetic analysis (68).

The increased sensitivity of state-of-the-art PET scanners and new reconstruction algorithms have provided new possibilities. Traditionally, \[^{15}\text{O}]\text{H}_2\text{O}\) studies were limited by noise, precluding generation of parametric images of MBF and thereby clinical acceptance. In combination with dedicated linearized methods for tracer kinetic analysis, increased scanner sensitivity provides a means to perform kinetic analyses on a voxel-by-voxel basis. The resulting parametric images show a kinetic parameter, such as MBF, for each voxel enabling both visual and quantitative assessments of the parameter of interest at the maximal spatial resolution. In addition, parametric images can be fused with CT images, showing all necessary information (i.e. functional and anatomical) in a single image (Figure 1.6).

1.5 Outline of the thesis

The aim of this thesis was to evaluate the feasibility of routine absolute quantification at the voxel level of several physiological processes in the myocardium: myocardial blood flow (Chapter 2, 3, 4, 6), viability (Chapter 2, 5), oxidative metabolism (Chapter 9) and sympathetic innervation (Chapter 7 8, 9, 10).

Chapter 2 gives an overview of the techniques used for quantification of MBF using \[^{15}\text{O}]\text{H}_2\text{O}\). This includes the mathematical basis for calculating parametric images of both MBF and perfusable tissue index (PTI).

Chapter 3 describes the validation of (semi-) automated generation of parametric images of MBF. This required linearization of the kinetic model and this was performed using a basis function approach. First, several segmentation algorithms for automatically extracting image derived input functions were evaluated. Then, quantitative results obtained directly from parametric images were compared with results obtained using the gold standard for curve fitting, required for kinetic modeling.

Chapter 4 describes a method that enables MBF to be calculated without
using a low-dose CT scan for attenuation. For all other MBF radiotracers, MBF is derived from the rate of uptake and therefore absolute scaling of PET data, requiring attenuation correction, is essential. Patient motion between PET and CT may affect MBF measurements. In contrast, for \[^{15}\text{O}]\text{H}_2\text{O}, MBF is estimated from radiotracer washout and therefore the low-dose CT scan is not required as absolute scaling is not essential. To validate this concept, quantitative accuracy of MBF obtained without attenuation was compared with MBF obtained with attenuation correction.

**Chapter 5** shows validation of PTI obtained directly from a single \[^{15}\text{O}]\text{H}_2\text{O} PET/CT scan. Instead of using \[^{15}\text{O}]\text{CO} to estimate blood volume, parametric images of blood volume fractions obtained using \[^{15}\text{O}]\text{H}_2\text{O} were used and validated using those obtained using \[^{15}\text{O}]\text{CO}. This makes the need for an additional \[^{15}\text{O}]\text{CO} scan obsolete.

**Chapter 6** contains a clinical comparison of two software packages, Cardiac VUer and Carimas, in clinical use for quantification of MBF as measured with \[^{15}\text{O}]\text{H}_2\text{O}. Differences in exact implementation exist between software packages and, for quantitative MBF to be widely accepted in a clinical setting, obtained values should be independent of the software package used.

In **Chapter 7**, the optimal kinetic model for quantification of \[^{11}\text{C}]\text{HED} was assessed. Analyses were performed using the gold standard for plasma...
input functions, i.e. an on-line blood sampler with metabolite corrections based on arterial blood. Several kinetic models were assessed for both clinical and simulated data. Then, the quantitative accuracy of several simplifications, such as retention index, standardized uptake values and the use of a population averaged metabolite correction, were assessed.

**Chapter 8** continues to evaluate additional simplifications for quantification of $^{11}$C-HED, the image-derived input function and the use of venous blood samples for metabolite correction. Both time-of-flight and non time-of-flight reconstructions with normal and Monte Carlo based scatter scaling were evaluated for quantitative accuracy of the image derived input function. In addition, quantitative accuracy of venous metabolite corrections were assessed both for unprocessed and converted venous blood data.

**Chapter 9** shows the validation of parametric images of the reversible one and two tissue models for $^{11}$C-HED and of the reversible one tissue model for $^{11}$C-acetate for both clinical and simulated data. In addition, new analysis software capable of incorporating parametric images in the definition of myocardial segments and analysing these images was compared with another analysis software package used for analysis of $^{11}$C-HED and $^{11}$C-acetate.

In **Chapter 10**, estimates of MBF based on $^{15}$O-H$_2$O and of the unidirectional uptake rate $K_1$ of $^{11}$C-HED were compared for the definition of defect areas, defined as the area of the left ventricle with MBF below a certain cut-off value. Clinically, a mismatch between innervation as assessed with $^{11}$C-HED and MBF may play a key role in predicting ventricular arrhythmias. Using $K_1$ as approximation of MBF may eliminate the need for an additional $^{15}$O-H$_2$O scan. First, the relationship between $K_1$ and MBF was assessed. Then, for various cut-off values, size and location of the defect area based on both $K_1$ and MBF were compared.

Finally, **Chapter 11** provides a summary and discussion of the results of this thesis.