Quantification and data optimisation of heart and brain studies in conventional nuclear medicine
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1. Introduction and outline of the thesis

Introduction

After the introduction of planar nuclear medicine images obtained with the Anger gamma camera (1957) and connection to a computer system (early 1970s), attempts have been made to enhance the quality of the scintigrams by filtering and noise subtraction (1,2). Using manual or automatic regions of interest on static or dynamic images, quantitative analysis of the radiopharmaceutical distribution led to the development of nuclear medicine procedures for many organs. Quantification reduces the inter- and intra-observer variability and improves the sensitivity and specificity of the nuclear medicine procedures (3). Using planar imaging, the superimposition of activity in front and behind the organ results in decreased image contrast and prevents accurate quantitative measurements. At the end of the 1970s three-dimensional information of the radionuclide distribution in humans was obtained by means of single photon emission computed tomography (SPECT) (4-6).

The ultimate goal was to quantify the absolute distribution of radioactivity. To achieve this goal many obstacles need to be overcome, some inherent to the gamma camera and planar acquisition, others to the tomographic reconstruction (7-11). In SPECT, photon absorption and scatter, particularly in the chest, produce regional inhomogeneities. Poor attenuation maps and misalignment between transmission and emission data also influence quantitative measurements (12). Step by step, solutions appear in literature and the new generation gamma cameras permit correction for photon absorption and scatter (13). In spite of all that, some physical properties hamper accurate quantification.

In the next paragraph physical parameters of the gamma camera are summarised. Then their impact on different quantification methods is highlighted. Finally in the aim and outline of the thesis, the application of correction methods or alternative approaches necessary for quantification of heart and brain studies is mentioned.

Physical properties

Calibration

The first requirement of an imaging system is that the image of an object is independent of its position in the field of view. Originally this is not the case due to impurities in the crystal and variations in the response of the photomultipliers, affecting both the energy estimate and event localisation. Variations of energy, non-linearity and uniformity can be corrected by calibration measurements. Tomographic reconstruction needs additional calibration for the centre of rotation of the detectors (14-16).

Scatter

Due to a limited energy resolution, usually a 20% energy resolution is used. Therefore, scattered events can amount to 20% in a typical brain study and even to 40% of the total counts in a cardiac study. The nature of scatter is thus study dependant in a complex manner both on the composition of the patient, the distribution of the tracer and the collimator and detector characteristics. Scatter is nonstationary. In SPECT, these scattered events must be removed before attenuation correction or in some cases a reduced linear attenuation coefficient can be used (17-19).

Dead-time

The sensitivity of an imaging system is defined by the number of counts per unit time detected by the device for a unit activity in the source. Only a fraction of the photons passes through the collimator and is absorbed by the crystal. Some of these events are rejected depending on the setting.
of the photopeak window. Some of the events are lost because the system is still busy processing a previous event. The probability of this situation increases with higher activities. As a result of the dead time of the system, the detected counts do not rise linearly with the activity. With further increase of activity, a saturated stage and even drop in the detected count rate may be observed (20,21).

**Partial volume effect**

Planar and SPECT images have a characteristic resolution. Images of objects larger than 2x the full width at half maximum of the point spread function will reflect both the size and radioactive concentration of the object. However for smaller objects, the signal is blurred; so that the total counts is preserved although the activity per pixel is decreased. This effect, known as partial volume effect, is particularly severe for SPECT images of the brain. Textures are below the resolving power of the methodology and accurate determination of radioactive concentrations is impossible (22-24).

**Acquisition Parameters**

The acquisition matrix must be chosen in function of the detector size, and the obtained pixel size defines the spatial sampling. Optimally, the pixel size should be less than the FWHM / 3 e.g. about 3-4 mm for a SPECT system characterized by a 10-12 mm FWHM resolution. The angular sample is defined by the number of projections in 360°. In order to ensure similar spatial and angular sampling for the reconstruction region, the angular interval should be such that the arch length is equal to the spatial sampling interval. For the circumference of the brain, optimal angular sampling interval should be about 3°. In cardiac studies, due to larger detector distance the FWHM is higher and the heart is more in the centre of the reconstructed volume, so angular sampling between 4° and 6° is used (25-27).

**Reconstruction parameters**

Reconstructing the angular images by filtered backprojection needs filtering by a Ramp filter to correct for image blurring. This enhances however the high spatial frequency noise in the reconstructed image. To suppress this noise, filters with specific parameters defining the degree of smoothing of the image are used. This reduces the information in the reconstructed image (27-29).

**Quantification**

Quantification of radioactive tracer concentrations depends and is limited by previous mentioned factors. Quantification analysis can be subdivided in three subclasses: the measurement of size and volume of features within the image, the relative activity concentrations within regions and the absolute tracer concentration in units of MBq/ml.

**Size and volume**

Size measurements always require some kind of contour definitions. Accurate size measurements are limited by the finite resolution of the system and the statistical errors in the reconstruction. The accuracy of the edge detection algorithms depends on the signal-to-noise ratio and the contrast range within the image. The partial volume effect defined by the finite resolution of the imaging process requires a different threshold for different sized structures. System and user defined parameters influence size measurements. The user can effect the final resolution of the image by the choice of the collimator, the acquisition pixel size and the reconstruction filter.
Relative concentration

Quantification comparing total activity or concentrations within several regions is the most common method in nuclear medicine procedures. The amount of activity can also be expressed relative to the maximum activity or mean activity in the image or the study. Reference anatomic regions or control subjects are used. The choice of region of interest size and placement, the adequate definition of anatomical regions and the identification of the reference site are critical. Taking care, data obtained within one centre or between centres with identical equipment for acquisition and processing might be compared. For centres using different detector systems with different resolutions, different acquisitions protocols and reconstruction methods, results will almost certainly be different.

Comparing different activities supposes a uniform sensitivity of the imaging system. This is achieved by calibration. At high count rate activity linearity during dynamic acquisitions is no longer present and dead time corrections are obliged.

In myocardial perfusion studies profiles normalised to the maximum activity or the most normal region can be compared with those of normal subjects. The localisation, extent and severity of a defect can be calculated and compared between rest and stress studies.

In myocardial viability studies, the profile of perfusion with Tc99m-sestamibi can be compared to the profile obtained with I123-BMIPP. Even acquired separately a supplementary problem rises. In the photo-peak Iodine-123 considerably higher scatter is measured from high-energy photons. Moreover, the distribution of the tracers are different. The nature of scatter depends in a complex manner both on the distribution of the tracer and the collimator and detector characteristics. Scatter is non-stationary and adds background activity in the myocardial profile. Scatter correction must be applied for quantitative comparison of these different isotopes.

Absolute quantification

The elusive but ultimate goal of quantification in nuclear medicine is the measurement of absolute tracer concentration in units of MBq/ml or in % of the injected dose. This would take in account all centre specific problems and data become non-centre specific. Absolute quantification performed in a specific centre can also be used to prove that an anatomic region remains stable within different patients, groups or treatment and thus can be used further on as reference region in relative quantitative measurements.

Although not totally accurate, absolute quantification might also be a supplementary tool for studies where small organs are involved and relative quantification is hampered by a huge partial volume effect.

Aim of the thesis

The aim of this work was to obtain accurate quantitative measurements useful in clinical practice in some heart and brain nuclear medicine procedures, applied in our department.

In the development of each method several of the following steps have to be covered:
- investigate the appropriate physical characteristics
- optimise and / or correct for physical characteristics
- figure out a practical method useful for clinical practice
- determine the accuracy of the method
- apply the method in patient studies
Outline of the thesis.

Chapter 2. Determination of left ventricular ejection fraction by first pass and gated SPECT studies.

2.1 At high count rate activity linearity during dynamic acquisitions is no longer present and dead time corrections are required. The performance of a single crystal digital gamma camera was studied for the evaluation of the left ventricular function. Ultrashort-lived Iridium-191m permitted rapid, repeat first pass studies.

2.2 System and user defined parameters influence size measurements. The variability of left ventricular ejection fraction and volumes calculated by quantitative gated SPECT modifying the acquisition pixel size and the reconstruction filter was measured. The impact on normal and small-sized hearts calculated by different algorithms on several processing stations was studied.

2.3 First pass studies were applied in patients at increasing levels of exercise. Exercise myocardial perfusion and wall motion using $^{201}$Tl and $^{191}$Ir simultaneously was studied.

Chapter 3. Myocardial perfusion and viability of the heart

3.1.1 In myocardial studies profiles are normalised to the maximum activity or the most normal. We generated colour-coded polar maps to quantify the uptake of $^{99m}$Tc-sestaMIBI and $^{123}$I-BMIPP in chronically dysfunctional myocardium. The difference in extent and severity of a defect was compared with coronary anatomy and wall motion.

3.2.1 In the photo-peak of Iodine-123 a considerably higher scatter portion is measured than with Tc99m-sestaMIBI. The influence of high-energy photons on the spectrum of iodine-123 with low- and medium-energy collimators is studied and the consequences for imaging with 123I-labelled compounds in clinical practice discussed.

3.2.2 The influence of methodology on the presence and extent of mismatching between perfusion using $^{99m}$Tc-MIBI and metabolism using $^{123}$I-BMIPP in myocardial viability studies was investigated.

3.3 Several clinical applications were published taking into account the previous mentioned spectral analysis. Comparative quantification of $^{99m}$Tc-MIBI and $^{123}$I-BMIPP tomography predicted functional outcome in chronically ischaemic dysfunctional myocardium and after acute myocardial infarction. BMIPP imaging improved the value of sestamibi scintigraphy for predicting functional outcome in severe chronic ischaemic left ventricular dysfunction.

Chapter 4. Perfusion of the brain

4.1 A review of quantification of brain perfusion and cerebral blood flow was published in a textbook presenting an up-to-date and systematic approach of SPECT in the major neurological and psychiatric disorders.

4.2 We calculated the absolute technetium-99m hexamethylpropylene amine oxime (HMPAO) brain uptake and proved that the cerebellum remains stable within different patients, groups or treatment and can be used as reference region in relative quantitative measurements.
Parameters influencing the SPECT regional brain uptake of technetium-99m HMPAO were studied in volunteers and patients. The cerebellum was validated as a reference region for SPECT quantification in patients suffering from dementia of the Alzheimer type.

Chapter 5. Dopamine transporter imaging in the human brain

In a small organ like the striatum relative quantification is hampered by a huge partial volume effect. We developed a region of interest independent method. Using gamma camera calibration factors for the radio-ligand Iodine-123-FPCIT we transformed the striatal uptake in absolute quantification. Although not totally accurate, absolute quantification might also be a supplementary tool for inter-centre comparison.

References: