Characteristics of a new fully programmable blood sampling device for monitoring blood radioactivity during PET

Ronald Boellaard, Arthur van Lingen, Suzette C.M. van Balen, Bas G. Hoving, Adriaan A. Lammertsma

Clinical PET Centre, University Hospital Vrije Universiteit, P.O. Box 7057, 1007 MB, Amsterdam, The Netherlands

Received 19 June and in revised form 20 September 2000 / Published online: 16 November 2000

Abstract. The first performance tests of a new fully programmable blood sampling device for monitoring blood radioactivity during positron emission tomography (PET) are described. Blood is withdrawn through 1-mm internal diameter tubing using an infusion pump which can be operated at rates varying from 0 to 600 ml/h. Activity in blood is measured by a 6-cm-thick bismuth germanate crystal connected to a photomultiplier tube and multichannel analyser (MCA) which are positioned within 6 cm lead shielding. Positioning of the tubing is an exact and simple procedure. The minimal readout time of the MCA is 1 s. Two independent energy windows can be set. Operation of the pump and MCA is fully controlled by a PC, i.e. sampling time, interval time and pump rate can be varied at any time during the PET scan by user-defined scripts. A number of characteristics of the new system were studied, such as sensitivity, dead time, linearity, effect of background radiation and pump rate as a function of input pressure. In addition, dispersion was measured as a function of pump rate. Finally, first clinical results were compared with manual samples. The sensitivity equalled 0.7 and 0.2 cps/Bq for 511- and 1022-keV 30% energy windows, respectively, and the system dead time was 500 ns. The system remained linear within 2% with activity concentrations up to 2.5 MBq/cc. Short-term reproducibility was better than 3% for a 1-h period. Long-term reproducibility was about 5% (1SD), which was mainly caused by variation in the diameter of the tubing. If the device was positioned in such a way that maximum shielding was directed towards the patient, the effects of background radiation from the patient on the measured activity concentration for clinically relevant conditions was minimal (<3%). Pump rate varied with input pressure, but remained constant for a given pressure. Dispersion constants smaller than 0.14 s^{-1} were observed for pump rates higher than 300 ml/h, indicating that the system dispersion is small. Clinical data showed an excellent agreement to within 3% (1SD) between the results obtained with the new system and manual samples. With the continuous blood sampler radioactivity in blood can be measured accurately during the entire course of the PET scan. Furthermore, the system is fully programmable allowing adjustment of all parameters during a single PET scan.

Keywords: Positron emission tomography – Arterial blood radioactivity – Input function

Eur J Nucl Med (2001) 28:81–89
DOI 10.1007/s002590000405

Introduction

Quantitative analysis of dynamic positron emission tomography (PET) data requires accurate measurements not only of the tissue response curves but also of the input function, usually derived from arterial blood [1]. The time course of blood radioactivity can be determined either using rapid manual sampling [2], preferably in combination with an automated handling system [3], or using automatic devices [4].

The first main disadvantage of manual sampling is the limited time resolution with which the samples can be drawn, e.g. once every 5 s, which limits the accuracy of data analysis and hampers corrections for delay and dispersion during kinetic modelling. Secondly, manual sampling leads to a high workload. To overcome these drawbacks, Graham and Lewellen developed a system which automatically collects discrete blood samples with a high speed of 1 sample per 2 s [4]. The activity in these discrete blood samples is then counted afterwards. Andersson and Schneider [3] described a fully automated system for handling of discrete blood, thereby minimizing the workload for measuring the activity in whole blood and plasma samples.

As an alternative to manual sampling, Nelson et al. [5] developed a non-invasive device for monitoring arterial blood activity in oxygen-15 (half-life = 122 s) water studies. In this study a probe was positioned near the superior lobe of the lung and the input function was derived from the measured variation of the photon flux.

Accurate results with the non-invasive monitor were only obtained after carefully correcting for background radiation and verification of the correct positioning of the probe. Furthermore, an additional online calibration was needed. Finally, this system could not be used for radioligand studies, which require blood metabolite analysis.

In order to directly obtain the input function, several investigators have developed continuous flow-through detectors [6, 7, 8, 9, 10, 11]. These systems require fewer personnel and are less error prone. Initially, plastic scintillator flow-through detection systems were applied by Hutchins et al. [6] and Kanno et al. [8]. Plastic scintillators are based on the detection of positrons. The dimension of the scintillator is adjusted in such way that it matches the range of the emitted positrons, at the same time minimizing the detection efficiency of 511-keV photons. Because the range of positrons depends on the isotope, these systems need to be calibrated for each isotope separately and the detector has a relatively large variation in geometrical sensitivity.

More recently, several flow-through systems have been developed based on the detection of annihilation photons. Nelson et al. [9] developed a flow-through system based on the detection of the 511-keV photons using an NaI crystal. Ranicar et al. [10] developed a system using a bismuth germanate (BGO) crystal and a peristaltic pump. The detection system was fully automated using a PC, allowing continuous recording of blood radioactivity using the 1022-keV sum peak. The pump, however, was not integrated into this system. Votaw and Shulman [11] recently described a commercially available system based on coincidence detection. This system consists of two BGO crystals operating in coincidence. BGO was used for its high stopping power and good counting properties. Since background radiation is rejected by coincidence counting, the system can be provided with minimal shielding and may be placed in the close vicinity of the patient. Votaw and Shulman [11] showed that this device had excellent counting characteristics and good sensitivity. The system is commercially available, but a disadvantage is that a syringe pump must be supplied by the user. In other words, not all components of the system are fully integrated. In addition, the measurement of the input function is limited to about 5 min, depending on the withdrawal speed.

In the present study, the characteristics of a new fully automated blood sampling device (Veenstra Instruments, The Netherlands) were measured. The system is based on the detection of 511-keV annihilation photons using a BGO crystal, but it is not equipped with coincidence detection. By applying two separate energy windows, data can be collected in a 511-keV singles peak and in a 1022-keV sum peak, similar to the system of Ranicar et al. [10]. The main advantage of this system is that operation of all separate components of the system (detector and pump) is fully integrated and programmable by the user, i.e. both detector and pump are operated using a PC with dedicated software. Sample duration, sample interval and pump rate can be varied during the entire course of the PET study. The variation of these parameters is controlled by scripts so that intervention of personnel during scanning is not required. However, pump operation can always be manually overruled if required for safety reasons. Finally, the entire system is commercially available and can be used as supplied without the need for installing additional components such as the pump or for writing software for data acquisition and storage.

Materials and methods

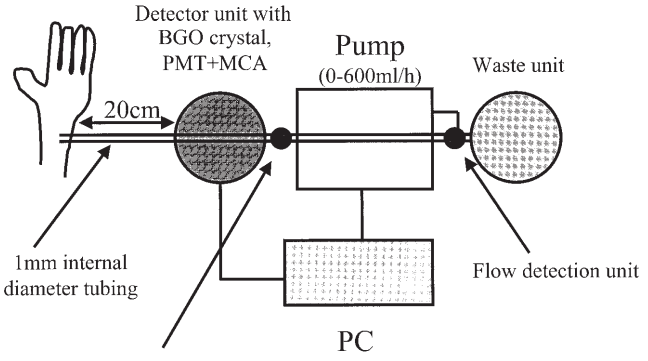
Description of blood sampling device

The automatic blood sampler (Veenstra Instruments) consists of a detector unit, a pump with a flow detection device, a waste unit and a PC. The entire system is mounted on a mobile cart. All components can be replaced separately in case of failure. In case of pump failure, however, it should be noted that although use is made of a commercially available infusion pump, it has been modified by the manufacturer to guarantee unidirectional flow, i.e. other infusion pumps cannot be used without this modification. The present commercial system complies with IEC 601 requirements regarding electro-mechanical safety, and recently the manufacturer has applied for CE certification of the system. A schematic drawing of the system is given in Fig. 1a, and a photograph of the sampler is shown in Fig. 1b.

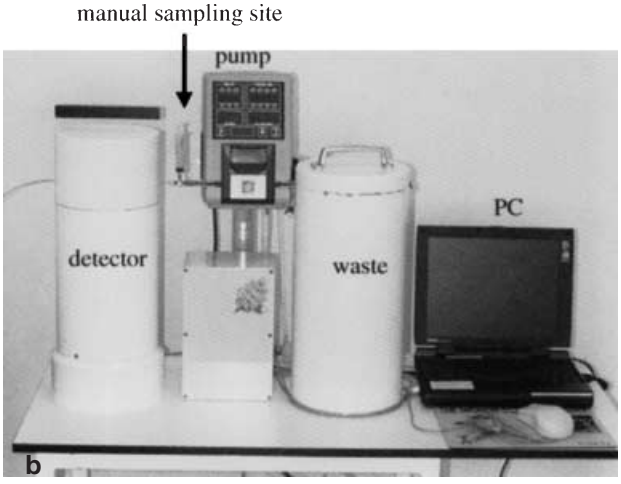
The detector unit (1c) consists of a 6-cm-diameter BGO crystal which is coupled to a photomultiplier tube (PMT) and multichannel analyser (MCA). Crystal, PMT, MCA and high-voltage power supply are all positioned within 6-cm lead shielding. A narrow slit opening of 3 mm is made in both crystal and shielding for easy and reproducible positioning of the tubing. The MCA can be set to collect counts with a minimum sample duration of 1 s. During acquisition, counts can be sorted by the MCA into 512, 1024 or 2048 energy channels as selected by the user. Once sample acquisition is completed, the entire spectrum is send to the PC for further analysis. At present 1 s is required to send the spectrum to the PC, thereby limiting the maximum sample rate to 1 sample per 2 s. Apart from the entire spectrum, the MCA also collects counts within a so-called fast channel. This channel collects all counts without energy discrimination and has negligible dead time characteristics (<500 ns). Data obtained with the fast channel are used for dead time correction of the spectrum (see below).

Blood is withdrawn from the patient through 1-mm inner diameter tubing using a peristaltic pump. The pump is equipped with a flow detection unit, which interrupts operation of the pump when the flow through the tubing is reduced by more than 30%. In this case an audible alarm signal is given. The pump is unidirectional, i.e. blood flow towards the patient is not possible. Pump rates can be varied from 0 to 600 ml/h (0–10 ml/min) in steps of 1 ml/h. Operation of the pump is controlled by the PC, but may always be overruled manually.

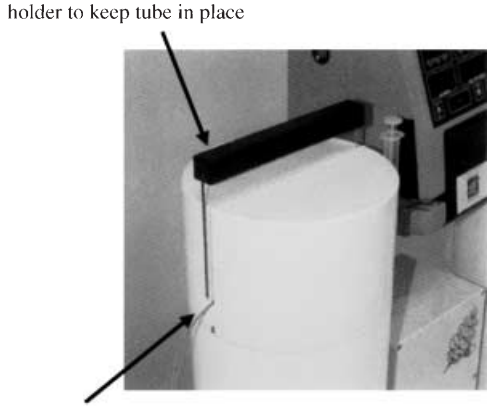
The system is equipped with a PC running under Windows95. The interface between PC and detector or pump has been realized through an RS-232 connection. Dedicated software, needed for operating the detector and pump and for data storage, is provided by the manufacturer. Sampling duration and interval as well as pump rate are controlled by the program during the entire study



a manual sampling site



b



c

Fig. 1. a Schematic drawing of the system indicating various parts of the automatic blood sampling device. **b** Photograph of the sampler. **c** Close-up photograph of the detector, showing simple and exact positioning of tubing in the slit opening of the detector

period. Furthermore, the program selects the two user-defined energy windows and the user-defined window widths.

For patient studies a user-defined script must be supplied to the program. This script is a text file consisting of a sequence of commands. These commands describe sample duration and interval of the MCA and the pump rate, and indicate when the program has to collect and process the data. A list of commands and their meaning is given in Table 1. Once the spectrum and fast channel data of a sample have been acquired by the MCA and transferred to the PC, the program starts processing these data, i.e. four numbers are calculated and stored into an output file: (1) total number of counts in window 1 (e.g. the 511-keV window); (2) total number of counts in window 2 (e.g. the 1022-keV window); (3) total number of counts in the entire spectrum, called the output counts; and (4) number of counts measured within the fast channel, called input counts. In addition, time of acquisition is written to the output file.

The ratio of output counts and input counts can be used to perform a dead time correction of the data in each energy window. The dead time-corrected number of counts, $Win_{1,2}^{Dtcorr}$, is given by:

$$Win_{1,2}^{Dtcorr} = Win_{1,2} \times IC/OC. \quad (1)$$

where $Win_{1,2}$ equals the number of counts in window 1 or 2, IC equals the number of input counts and OC equals the number of output counts. This relation can be easily understood. The fast channel collects all counts without energy discrimination and with essentially no dead time losses. In fact, the system software corrects for the 500 ns dead time of the fast channel using a paralysable model. The input counts therefore represent the total number of counts which would have been measured in the spectrum if the MCA had no dead time. The output counts are obtained by summing the entire spectrum, which suffers from MCA dead time losses. The ratio of input to output counts therefore equals the dead time correction required for the MCA spectrum. This correction can be performed online and offline.

Clinical use

For daily clinical routine use, a number of tests are performed in order to assure correct operation of the system. First, every morning an energy spectrum is acquired using a germanium-68 needle source. This is used to verify the position of both 511- and 1022-keV peaks. When a shift of the spectrum is observed, the spectrum can be adjusted by changing either the energy windows or the high voltage. To date, after 2 years of operation, adjustment was only required in the event of large room temperature variation or high humidity, i.e. when the system was used in a laboratory environment. Under normal clinical conditions (air-conditioned scanning room), however, the system has been stable over periods of 2 months. A second test is performed to verify the communication of both MCA and pump with the PC. As the setup time of the MCA is approximately 20 s, communication between MCA and PC may be disturbed when a measurement is started within 20 s after switching on the system. Therefore, a dry run is performed immediately prior to each patient study to check communication of MCA and pump with the PC. To date the system has worked correctly, provided the 20-s initialization period of the MCA is observed. Whenever communication errors occur, patient measurements may proceed simply by resetting the system.

For patient measurements the system is placed directly next to the scanner bed, allowing the use of short tubing of less than 50 cm between patient and detector unit. Because no shielding is present in front of the slit opening of the detector, the system is positioned in such a way that the direction of the slit is parallel to the patient longitudinal axis, thereby avoiding direct exposure of the BGO crystal from background radiation originating from the

Table 1. Script commands and their meanings

Script command	Meaning of command
OPEN_REPORT “filename”	Opens an output file
REPORT_COMMENT “xx”	Writes “xx” to output file
MCA_PARAMETERS	Writes the MCA parameters, such as HV settings, to output file
SET_TOTAL_ML	Sets maximum volume to be pumped
START_PUMP xx	Starts pump with pump rate xx ml/h
STOP_PUMP	Stops the pump
DATE_TIME	Writes date and time to output file
SAMPLE xx	Acquires a sample during xx s
GET_SPECTRUM	Sends spectrum data from MCA to PC
READ_WINDOW 1,2	Calculates number of counts within window 1,2
STORE_RESULT	Writes data of window 1,2 to output file
DEAD_TIME_DATA	Writes info about dead time corrections to output file
WAIT xx	Pauses readout of MCA during xx ms
PROMPT “xx”	Shows dialog box with message “xx”, press OK to continue measurement

patient. After carefully positioning the system and connecting to the patient, a script is executed to start the measurement. A limitation of the present software is that all measurement scripts have to be edited by the user. In order to store the data the first line of the measurement script, indicating the output data file, needs to be edited to indicate a specific output file name, as indicated in Table 1. Because this procedure is error prone and may result in loss of old data, additional in-house software was developed to generate patient-specific measurement scripts and output files.

A typical script would consist of 1-s samples during the first 5 min, followed by 2-s samples from 5 to 10 min, 5-s samples from 10 to 30 min and 10- to 30-s samples from 30 min onwards. The pump rate is usually set to 300 ml/h (5 ml/min) during the first 5 min and is then adjusted automatically to 100 ml/h afterwards. Manual samples are taken at set times immediately behind the detector. These samples are used for calibration purposes, for estimation of whole blood to plasma ratios, and for metabolite analysis as described previously [3, 12]. After each sample, the tubing is flushed with heparinized saline to prevent clotting. These flushing periods are also used to check whether the detector count rate has gone to zero, i.e. as a quality control procedure for the presence of activity sticking to the tube wall [12]. During manual sampling, pump operation is temporarily interrupted by the user, but is controlled again by the PC afterwards. All data, i.e. the number of counts in the first (511-keV) and second (1022-keV) energy windows, the total number of counts in the spectrum and the fast channel data or input counts, are stored in an output file together with acquisition time, sample duration and dead time correction factor. Calibration and decay correction and correction for sample duration need to be applied afterwards to convert counts per sample to activity concentration. To overcome these limitations additional software was developed to automatically format the data file, to apply calibration factors and decay and dead time correction, and to take sample duration into account. The need to write additional software by the user is a limitation of the current (prototype) system. It is expected, however, that various modifications described here will be incorporated in the next release of the system software.

For patient studies, dead time correction is performed offline. With low activity concentrations and for short sample durations, the number of counts collected in each energy window and the fast channel can be small (e.g. <100). Using the dead time correction as given with Eq. 1 will then result in an increased uncertainty, while for low activity concentrations (<300 kBq/cc), dead time may be neglected. Therefore, dead time correction using Eq. 1 is applied when the number of counts collected in the fast channel exceeds 3,000. By using such a limit, dead time correction with Eq. 1 is performed only when the activity concentration in blood is higher than 60 kBq/cc for a 1-s sample. In order to apply this approach it is necessary to perform the dead time correction offline.

Measurements

First, a number of characteristics of the detector unit were studied: linearity and/or dead time characteristics, accuracy of dead time correction, linearity with sample duration, sensitivity, short- and long-term reproducibility, effects of background radiation. Next, operation of the pump, i.e. linearity of pump rate as a function of defined pump rate and input pressure was determined. Subsequently, the dispersion of the system was measured as a function of pump rate. Finally, first clinical results were compared with manual samples. All measurements were performed with 30% energy windows around both the 511-keV and 1022-keV sum peaks.

Detector characteristics. To measure linearity with activity concentration and dead time characteristics of the detector, the 1-mm inner diameter tube was filled with a high activity concentration of 20 MBq/cc fluorine-18 fluorodeoxyglucose (^{18}F-FDG) (half-life of ^{18}F=110 min) and positioned within the slit opening of the detector. This activity concentration was about 40 times higher than normally encountered during patient measurements (<500 kBq/cc). Samples were acquired during a period of 36 h. Sample duration was set to 10 min in order to collect a sufficient number of counts at the end of the measurement period. Samples were taken at 20-min intervals. The entire measurement was performed twice, with and without online dead time correction, in order to validate the online correction procedure as implemented by the manufacturer. The response of the system at low activities was used to estimate the sensitivity of the detector.

As electronically controlling and reading out the MCA may require some overhead time, the linearity of the system with sample duration was investigated. For this measurement the tube was

filled with an activity concentration of about 60 kBq/cc ^{18}F-FDG. The measurement procedure started with 100 samples of 1 s duration, followed with 50 samples of 2 s, 50 samples of 5 s, 50 samples of 10 s and 10 samples of 30 s. This range of sample durations covers the clinically applied range. The effects of sample duration on the acquired data were determined by comparing the average value for each sample duration after (online) dead time and (offline) decay correction.

Short-term reproducibility was assessed by collecting ten samples of 10 s duration during a period of 1 h. The 1-mm inner diameter tube was filled with a high activity concentration of 100 kBq/cc ^{18}F solution for statistical reasons. Results were compared after dead time and decay correction. Long-term reproducibility was determined by measuring the response of the detector with a 60-s sample every 2 weeks using a "calibration" ^{18}F solution (calibration of the blood sampling device is part of the routine calibration procedure also including PET scanner, dose calibrators and well counters). Manual samples were also taken from the ^{18}F solution and measured with a well counter to determine the exact activity concentration of the solution. Calibration factors for the 511- and 1022-keV windows are defined as the ratio between the activity concentration (Bq/cc) and the cps per energy window, again after dead time and decay correction. The variation of the calibration factor over time is used as a measure for long-term reproducibility. An alternative would be the use of a ^{68}Ge source for assessment of long-term reproducibility. However, because the diameter of the needle source was too large to fit within the slit opening of the detector, it could not be used for the latter purpose. The daily verification of the absence of drift of the energy spectrum was not hampered by the ^{68}Ge source size as it was placed directly on top of the detector, allowing the acquisition of an energy spectrum containing both a (singles) 511-keV and a (randoms) 1022-keV peak.

The BGO crystal and PMT are shielded with approximately 6 cm lead. Because data are not acquired with coincidence detection, large effects of background radiation may still be expected for the 511-keV window data. To determine the effects of background radiation, a 37 MBq ^{18}F source was positioned at several locations in relation to the detector unit as indicated in Fig. 2, varying both distance and position with respect to slit opening, and with no activity present in the tubing. For each position the number of counts within the 511- and 1022-keV windows was measured with 5-min samples. To estimate the relative effect of background radiation, the experiment was repeated with a 100 kBq/cc ^{18}F solution within the tube. In addition to these experiments, the effect of background radiation during a dynamic ^{18}F-FDG brain scan was also measured. During this latter experiment the tubing was not connected to the patient, i.e. no arterial blood was withdrawn.

Pump characteristics. The blood sampler is equipped with a peristaltic infusion pump, which is now used to withdraw blood from the patient. Because the pump is developed to infuse liquid into the patient rather than to withdraw arterial blood from the patient, correct operation of the pump under these different conditions needs to be validated. Normally the infusion bag is positioned about 50 cm above the infusion pump. It can therefore be expected that the pump is developed to operate correctly for the indicated pump rate when the input pressure equals 37 mmHg.

To determine the effect of input pressure on pump operation, the 1-mm inner diameter tube was connected to a 2-m infusion line (approximately 3 mm inner diameter) and a 250-ml syringe. Tube, infusion line and syringe were filled with water. By varying the height between syringe and pump the input pressure to the pump was varied. The actual pump rate was determined by collecting the water at the end of the narrow tube into a beaker and measuring the weight of the pumped volume every minute during a period of 10 min. A schematic drawing of this experiment is given in Fig. 3. Input pressures of 0, 50 and 100 mmHg (0, 67 and 135 cm H_2O) were applied and pump operation was tested for pump rates of 50, 100 and 300 ml/h.

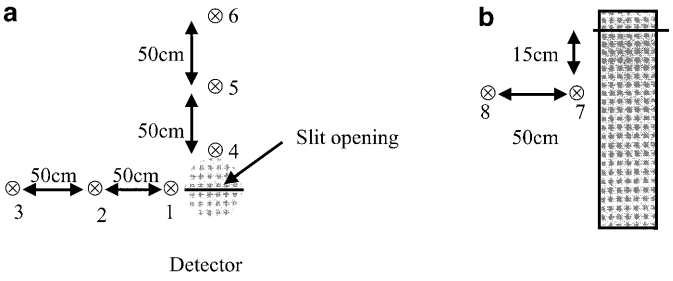


Fig. 2a, b. Setup of shielding experiment showing the positions of a 37 MBq ^{18}F source (⊗) relative to the detector unit. **a** The background source was positioned at 0, 50 or 100 cm from the detector both in front of and perpendicular to the slit opening. **b** The background source was positioned in front of and 15 cm below the slit opening.

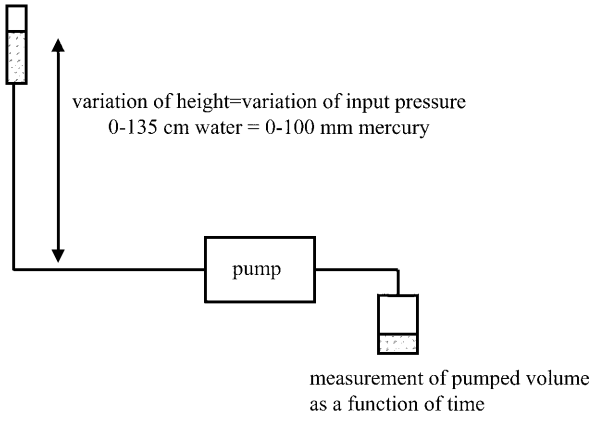


Fig. 3. Setup for pump rate measurement. Input pressure was varied by changing the height of the water column relative to the pump. A water column of 135 cm corresponds to an input pressure of 100 mmHg. The total pumped volume was determined by measuring the weight of water pumped into a beaker (as a function of time)

Dispersion. Dispersion was measured as the response to both a step-up and a step-down function of the activity concentration using both blood and water, using the procedure described by Votaw and Shulman [11]. Assuming that dispersion can be modelled with a single exponential function, both Votaw and Shulman and Iida et al. [13] showed that the dispersion constant can be determined by measuring the response of the system to a step-up or step-down function of the activity concentration. The dispersion function has been described extensively in the literature [13, 14, 15]; therefore here only the measurement procedure is given.

A step-up function was created by withdrawing non-radioactive blood or water from a beaker and, once the beaker was almost empty, by adding quickly a relatively large volume of blood or water with a high activity concentration to the beaker. The step-

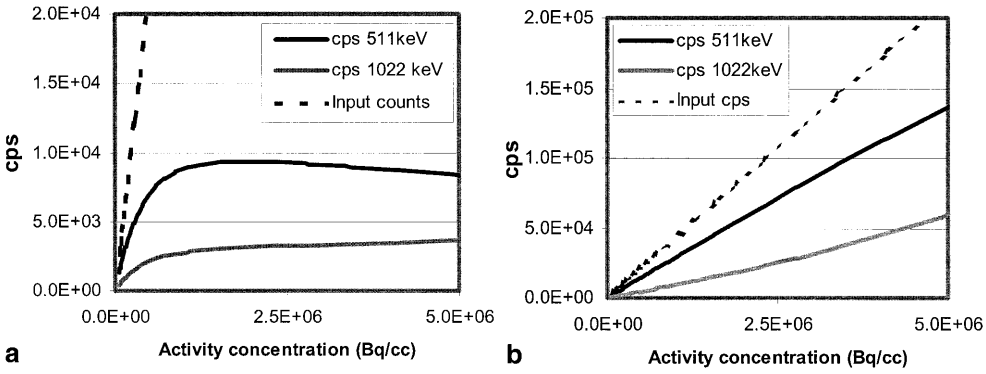


Fig. 4. Linearity of the 1022-keV (*grey curve*) and 511-keV (*solid black curve*) windows and the fast channel (*upper dotted curve*) with activity concentration measured **a** without dead time correction and **b** with online dead time correction. *cps*, Counts per second

down function was obtained by following the reciprocal procedure. During these experiments samples of 1 s duration were measured continuously and pump rates of 50, 100 and 300 ml/h were applied. Results were fitted using a single exponential function as described by Iida et al. [13].

First clinical measurements. First clinical results with the blood sampler were obtained for five dynamic ^{18}F-FDG and two carbon-11 flumazenil studies, which were carried out within ongoing clinical protocols, i.e. these studies have been approved by the medical ethics committee of the University Hospital Vrije Universiteit, Amsterdam, The Netherlands. Five manual samples were taken at approximately 5, 10, 20, 30 and 50 min after the start of the PET scan. These samples were measured in a well counter. The sampler curve was corrected for dead time and decay and then calibrated. The corrected sampler curve was then compared with manual samples.

Results and discussion

Detector characteristics

In Fig. 4a results of the linearity experiment without dead time correction are shown. It was found that the number of counts collected in the fast channel, the input counts, was linear to within 2% with activity concentrations up to 10 MBq/cc, which is well beyond the clinically relevant range (0–500 kBq/cc). Data obtained with both energy windows were linear with activity concentrations up to 300 kBq/cc, which would be an insufficient range for clinical studies. Data acquired within the 511-keV energy window showed a maximum count rate of 9.3 kHz at an activity concentration of 1.9 MBq/cc. At higher activity concentrations the count rate measured within this energy window decreased owing to increasing dead time. For the 1022-keV data no maximum count rate was found as its signal continuously increased with activity in a non-linear manner. The 511-keV data suggest that the dead time characteristics of the MCA can be described by the paralysable model. Figure 4b shows the results obtained when the data collected in both energy windows were corrected for dead time using the fast channel approach and Eq. 1. Using this correction, linearity of the signals of both energy windows remained within 2% up to activity concentrations of 2.5 MBq/cc. At activity concentrations higher than 2.5 MBq/cc, the dead time correction based on the input counts failed, although the data of the fast channel were still linear with activity concentration. This was caused by deterioration of the measured spectrum due to the effects of pulse pile-up and overflow of the MCA. The latter effect also explains the continuous but non-linear increase in the 1022-keV signal with activity, because the deterioration occurred mainly at the higher energy channels (>700 keV). Since deterioration of the spectrum occurred at activity concentrations higher than those normally encountered in patient studies (<500 kBq), it can be concluded that the linearity of the system is sufficient for clinical applications provided dead time correction using the fast channel approach is applied.

At low activities the sensitivity of the detector (without dead time correction) equalled 0.023 cps/Bq per cc and 0.0067 cps/Bq per cc for the 511- and 1022-keV peaks, respectively. Assuming that the detector "sees" only 6 cm of the 1-mm inner diameter tubing, the sensitivity equalled 0.70 cps/Bq and 0.20 cps/Bq for both energy windows. The ratio of the sensitivities of the 511- and 1022-keV windows was equal to about 3.4 in the absence of background radiation. This ratio can be used to validate the accuracy of the collected data during patient studies, as will be discussed later.

The average number of counts collected within both energy windows and the fast channel as a function of the sample duration after dead time correction remained constant to within 1.5% for each sample duration. Therefore, overhead and processing time of the MCA may be neglected and does not have any effects on the response of the system.

Measurements of short- and long-term reproducibility indicated that the short-term reproducibility was within 3%, i.e. the number of counts of ten samples, each of 10 s, measured within a 1-h period did not differ by more than 3% using the same tubing. Poisson statistics could account for about 1.5% of this 3% deviation. Long-term reproducibility was estimated to be within 5% (1SD) based on the variation of the calibration factor over a period of 3 months. The observed long-term reproducibility of 5% (1SD) seems rather poor. However, measurements

Table 2. Effects of a 37 MBq ^{18}F background source on the measured count rate with and without activity in the detector for various locations relative to the detector

Position index	Cps 511 keV	Cps 1022 keV	Cps 511 keV	CPS 1022 keV
	No activity	No activity		
1	2,312	450	2,113	437
2	933	0.7	1,300	396
3	185	0.2	1,215	391
4	150	4.3	1,445	433
5	65	0.3	1,281	408
6	21	0.1	1,242	399
7	1.6	0.3	1,180	395
8	37	0.2	1,182	393

Position index corresponds with that shown in Fig. 2. The second and third columns present data obtained without activity (no activity) in the tubing, while the fourth and fifth columns show data obtained with 100 kBq/cc in the tubing
Cps, Counts per second

of long-term reproducibility were performed with different tubing sets and, therefore, were affected by possible variation of the inner diameter of the tubing. To assess this possibility the variation of the detector response for ten tubing sets each filled with an equal ^{18}F solution was studied. In this experiment. two out of the ten tubing sets showed a deviation of more than 5% (compared with the average of remaining eight tubing sets) in detector response, which is explained by variance in detected volume due to variation of the inner diameter of the tubing. It should be noted that detector response also appeared to be affected by room temperature. In practice, this is a minor problem as the system is used in a temperature-controlled scanning room. Nevertheless, due to possible effects of variation of tubing diameter, for accurate clinical studies, additional manual samples should be taken for online calibration. The remaining short-term reproducibility (<3%) is sufficient to accurately measure the blood radioactivity concentration in clinical studies.

Table 2 presents data of the shielding experiment. It can be seen that at position 1, i.e. directly in front of the slit opening of the detector, the number of counts in the 511-keV window was significantly higher than at other positions. Although this effect was much smaller for the 1022-keV window, it was still present. Similar results were found when the tubing was filled with 100 kBq/cc ^{18}F solution (4th and 5th columns). Since data in Table 2 were not corrected for dead time, the cps values with activity in the detector (columns 4 and 5) and with the background source at position 1 are similar to those given in the second and third columns. Data collected within the 1022-keV sum peak are based on simultaneous detection of two 511-keV photons so that it can be expected that this energy window is less sensitive for background radiation than the 511-keV window.

Measurement of background radiation without connecting the tube to a patient showed an average count rate of 55 cps in the 511-keV window and 2 cps in the 1022-keV window. On average, minimum count rates during measurement of the input function equal 250 and 75 cps in the 511- and 1022-keV windows, respectively. Background radiation (from the patient) might increase the signal of the 511-keV window up to about 20%, while the effect of background radiation on data collected within the 1022-keV window remains within 3%. These results indicate that the accuracy of the 511-keV data should always be validated using the ratio between data of both windows. Because only the 511-keV window is sensitive for background radiation, a constant ratio indicates that background radiation is minimal and that data of both 511- and 1022-keV windows can be combined to improve statistical accuracy. When a high background source is present during sampling, the 511-keV data should be discarded.

Additional shielding within and in front of the slit openings, which would further reduce the contribution of background radiation, is presently under development by the manufacturer. A maze-like arrangement of the slit would be preferable, but would require major modification of the detector's design. An alternative solution might be to tape the tubing to the detector casing, thereby removing direct exposure of the BGO crystal from those portions of the tubing located directly next to the detector. However, even with these adjustments, users should carefully validate whether effects of background radiation may be neglected. It should be noted that radiation from the patient might make a considerable contribution to the background radiation in the 511-keV energy window.

Pump characteristics

Operation of pump as a function of input pressure and pump rate is presented in Fig. 5. Best agreement between indicated and measured pump rate occurred with an input pressure corresponding to a water column of 50 cm. Measured pump rate was approximately 10% smaller than the indicated pump rate at 0 input pressure and about 5% larger at an input pressure resulting from a water column of 135 cm height. As infusion pumps are designed to pump infusion fluid from a bag which is usually positioned 50 cm above the pump, the good agreement between measured and set pump rate for this situation is clear. More importantly, within each experimental setup operation of the pump did not vary, as can be derived from the curves in Fig. 5. The measured pump characteristics therefore indicate that under clinical conditions the pump rate may vary between patients (due to variation of input pressure) but that it remains constant within a patient study. Therefore, it can be concluded that the pump is suitable for its current application as a small but constant deviation between indicated and actual pump rate does not have an effect on the shape of the measured input function.

Dispersion

In Fig. 6a and 6b, typical response curves of the dispersion measurement using blood are shown. The results obtained by fitting the response curves to a mono-exponential function are summarized in Table 3. These data indicate that the variation of the dispersion constant with pump rate was similar for both water and blood. Lower dispersion constants were found for blood, owing to the higher viscosity of blood compared with water. The discrepancy of the dispersion constants between the step-up and step-down measurements at higher flow rate is not understood, but may be caused by sticking of FDG to the tubing wall. With increasing pump rate the value of the dispersion constant increased, indicating that a high pump rate (300 ml/h or more) should be used to minimize the effect of dispersion at the beginning of a patient study when blood activity concentration varies strongly. At pump rates greater than 300 ml/h the dispersion constant is smaller than 7 s for both blood and water. The dispersion constant of 3.3 s at 600 ml/h is slightly larger than the dispersion constant of 1.9 s found for the Pico-count system, described by Votaw et al. [11]. In clinical practice, pump rates are usually set to 300 ml/h during the first 5 min of the measurement to minimize dispersion when blood radioactivity is changing rapidly. Because blood radioactivity varies slowly after 5 min, effects of dispersion are minimal and the pump rate can be set to 100 ml/h to limit the total amount of blood withdrawn from the patient. Pump rates lower than 100 ml/h should not be used to prevent clotting of blood within the tubing.

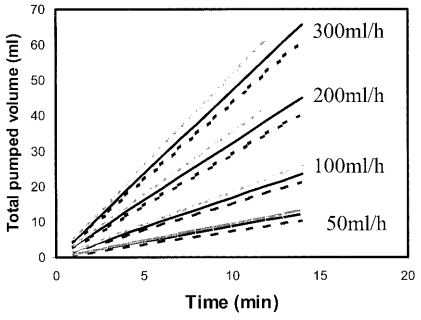


Fig. 5. Pump volume as a function of time for various pump rates (50, 100, 200 and 300 ml/h). Input pressures resulting from a water column height of 0 cm (*dashed line*), 65 cm (*solid black line*) and 135 cm (*grey line*) are presented

First clinical results

Clinical results were obtained for five patients injected with 370 MBq (10 mCi) ^{18}F-FDG and for two patients injected with 370 MBq (10 mCi) ^{11}C-flumazenil. Figure 7 shows the input function of an ^{18}F-FDG study measured with the sampler using both energy windows and the data obtained with manual samples. These figures demonstrate that data collected within both energy win-

Fig. 6. Typical response curves of the detector following **a** a step-down and **b** a step-up change in activity concentration of blood in the tubing for various pump rates. In **a** the upper curve was obtained with a pump rate of 50 ml/h, while in **b** the upper curve was acquired with a 600 ml/h pump rate. In each figure the equation of the dispersion response used to obtain the dispersion constants is presented

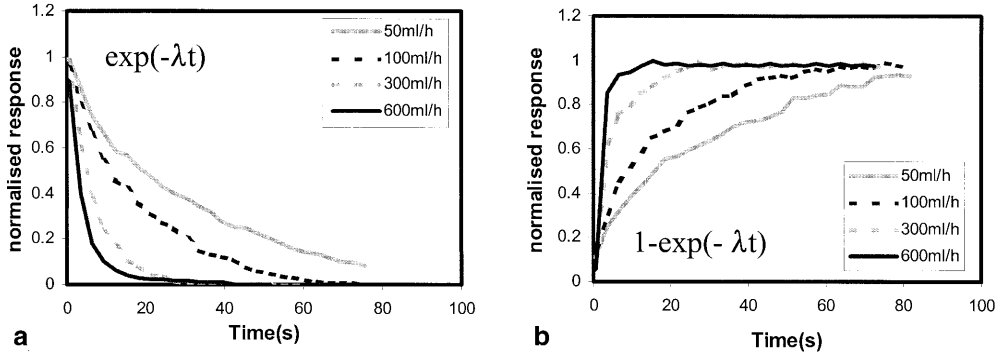


Table 3. Dispersion constants measured with water and blood according to a step-up or step-down change of activity in the tubing for various pump rates

Pump rate (ml/h)	Water step-up (s^{-1})	Water step-down (s^{-1})	Blood step-up (s^{-1})	Blood step-down (s^{-1})
50	0.04	0.03	0.03	0.03
100	0.07	0.07	0.06	0.06
300	0.25	0.21	0.19	0.14
600	0.60	0.35	0.45	0.30

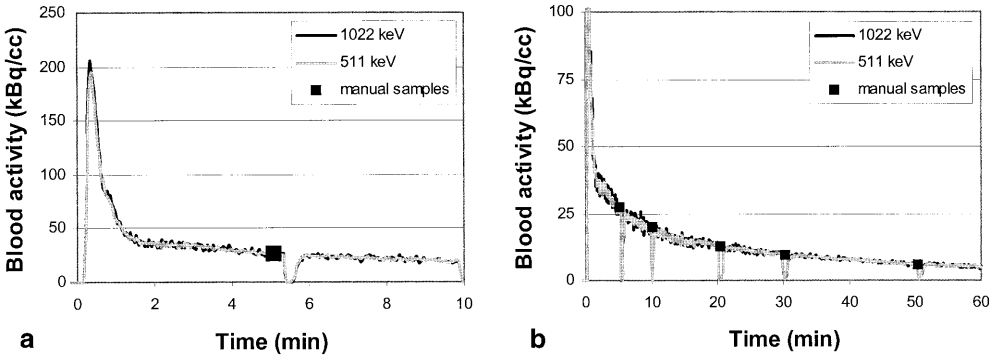


Fig. 7a, b. First clinical results. **a** The input function during the first 10 min of a dynamic ^{18}F-FDG study; **b** the input function over the entire study period. In addition, data acquired with manual samples are shown. Irregularities in the measured input function were caused by flushing the tubing with heparinized saline to prevent clotting immediately following a manual sample

dows correspond very well, indicating that the influence of background radiation is minimal (<3%). Nevertheless, it is still recommended to validate the data of the 511-keV window, as explained previously. Secondly, there is excellent agreement between the continuously measured input function and the activity concentration measured using the manual samples. After calibrating the data derived from the blood sampler, differences between measured input function and individual manual sample data were smaller than ±3% for all measured samples. The irregularities in the measured input function, occurring directly after each manual sample, are caused by flushing the tubing with heparinized saline [12]. Note that the dips return to zero, indicating that the ^{18}F-FDG activity does not stick to the tubing wall.

Conclusions

With the blood sampler (Veenstra Instruments) the radioactivity concentration in blood can be measured with a high degree of accuracy and reproducibility (<3%, 1SD). The system is fully programmable, allowing the user to adjust sampling rate, sampling time and pump rate during scanning. In order to limit the effects of background radiation from the patient (<3% of the signal in the 511-keV window), the detector should be carefully positioned to avoid direct exposure of the crystal through the slit opening. When operating the system with pump rates at or above 300 ml/h, the dispersion constant is smaller than 5 s. A disadvantage of the system is that after each sample acquisition about 1 s is needed to transfer the data from the MCA to the PC. The maximum sample rate is thereby limited to 1 sample (of 1 s) per 2 s.

Acknowledgements. The contribution and useful suggestions of Veenstra Instruments are gratefully acknowledged.

References

1. Lammertsma AA, Cunningham VJ, Deiber MP, et al. Combination of dynamic and integral methods for generating reproducible functional CBF images. *J Cereb Blood Flow Metab* 1990; 10:675–686.
2. Herscovitch P, Markham J, Raichle ME. Brain blood flow measured with intravenous H_2(15)O. I. Theory and error analysis. *J Nucl Med* 1983; 24:782–789.
3. Andersson JL, Schneider H. Design, construction and six years' experience of an integrated system for automated handling of discrete blood samples. *Eur J Nucl Med* 1998; 25:85–90.
4. Graham MM, Lewellen BL. High-speed automated discrete blood sampling for positron emission tomography. *J Nucl Med* 1993; 34:1357–1360.
5. Nelson AD, Miraldi F, Muzic RF Jr. et al. Noninvasive arterial monitor for quantitative oxygen-15-water blood flow studies. *J Nucl Med* 1993; 34:1000–1006.
6. Hutchins GD, Hichwa RD, Koeppe RA. A continuous flow input function detector for H_2(O-15) blood flow studies in positron emission tomography. *IEEE Nucl Sci* 1986; 33:546–549.
7. Eriksson L, Kanno I. Blood sampling devices and measurements. *Med Prog Technol* 1991; 17:249–257.
8. Kanno I, Iida H, Miura S, et al. A system for cerebral blood flow measurement using an $H_2{}^{15}O$ autoradiographic method and positron emission tomography. *J Cereb Blood Flow Metab* 1987; 7:143–153.
9. Nelson AD, Muzic RF, Miraldi F, et al. Continuous arterial positron monitor for quantitation in PET imaging. *Am J Physiol Imaging* 1990; 5:84–88.
10. Ranicar AS, Williams CW, Schnorr L, et al. The on-line monitoring of continuously withdrawn arterial blood during PET studies using a single BGO/photomultiplier assembly and non-stick tubing. *Med Prog Technol* 1991; 17:259–264.
11. Votaw JR, Shulman SD. Performance evaluation of the Pico-Count flow-through detector for use in cerebral blood flow PET studies. *J Nucl Med* 1998; 39:509–515.
12. Lammertsma AA, Bench CJ, Price GW, et al. Measurement of cerebral monoamine oxidase B activity using L-[^{11}C]deprenyl and dynamic positron emission tomography. *J Cereb Blood Flow Metab* 1991; 11:545–556.
13. Iida H, Kanno I, Miura S, et al. Error analysis of a quantitative cerebral blood flow measurement using H_2(15)O autoradiography and positron emission tomography, with respect to the dispersion of the input function. *J Cereb Blood Flow Metab* 1986; 6:536–545.
14. Meyer E. Simultaneous correction for tracer arrival delay and dispersion in CBF measurements by the $H_2{}^{15}O$ autoradiographic method and dynamic PET. *J Nucl Med* 1989; 30:1069–1078.
15. Lammertsma AA, Frackowiak RS, Hoffman JM, et al. The $C^{15}O_2$ build-up technique to measure regional cerebral blood flow and volume of distribution of water. *J Cereb Blood Flow Metab* 1989; 9:461–470.