Non-invasive quantification of cerebral glucose metabolism using Gjedde-Patlak plot and image-derived input function from the aorta

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A R T I C L E   I N F O

Keywords:
Cerebral glucose metabolism
CMRglc
\(^{18}\)F-FDG
PET
Positron emission tomography
Brain

A B S T R A C T

Introduction: We aimed at evaluating a Gjedde-Patlab plot and non-invasive image-derived input functions (IDIF) from the aorta to quantify cerebral glucose metabolic rate (CMRglc) in comparison to the reference standard based on sampling the arterial input function (AIF).

Method: Six healthy subjects received 200 MBq \(^{18}\)F-FDG simultaneously with the initiation of a three-part dynamic PET recording consisting of a 15 min-recording of the aorta, a 40 min-recording of the brain and finally 2 min-recording of the aorta. Simultaneously, the arterial \(^{18}\)F concentration was measured via arterial cannulation. Regions of interest were drawn in the aorta and the brain and time-activity curves extracted. The IDIF was obtained by fitting a triple exponential function to the aorta time-activity curve after the initial peak including the late aorta frame, thereby interpolating the arterial blood activity concentration during the brain scan. CMRglc was calculated from Gjedde-Patlab plots using AIF and IDIF, respectively and the predictive value was examined. Results from frontal cortex, insula, hippocampus and cerebellum were compared by paired t-test and agreement between the methods was analyzed by Bland-Altman plot statistics.

Results: There was a strong linear relationship and an excellent agreement between the methods (mean ± SD of CMRglcIDIF (μmol 100 g\(^{-1}\) min\(^{-1}\)), mean difference, mean relative difference, 95% limits of agreement): frontal cortex: 30.8 ± 3.3, 0.5, 2.2%, [-1.6:2.5], insula: 25.4 ± 2.2, 0.4, 2.4%, [-1.4:2.2], hippocampus: 16.9 ± 1.2, 0.4, 3.8%, [-1.1:2.0] and cerebellum: 23.4 ± 1.9, 0.5, 3.1%, [-1.4:2.5]).

Conclusion: We found excellent agreement between CMRglc obtained with an IDIF from the aorta and the reference standard with AIF. A non-invasive three-part dynamic \(^{18}\)F-FDG PET recording is feasible as a non-invasive alternative for reliable quantification of cerebral glucose metabolism in all scanner systems. This is useful in patients with presumed global cerebral changes owing to systemic disease or for the monitoring of treatment effects.

1. Introduction

The cerebral metabolism of glucose is vital for normal cognitive functioning. 2-\(^{18}\)F-fluoro-2-deoxy-D-glucose (\(^{18}\)F-FDG) positron emission tomography (PET) is a well-established method for evaluating cerebral metabolism, and the regional distribution of \(^{18}\)F-FDG relative to cerebellum, pons or the global level is routinely used in the work-up of dementia (Nobili et al., 2018). However, global cerebral disturbances are reported in a number of conditions affecting brain function, e.g., cardiac arrest (de Lange et al., 2012; Zhang et al., 2021), medical and non-medical treatment (Gejl et al., 2016; Henry et al., 2001; Schrekenberger et al., 1999), and traumatic brain damage (Bergsneider et al., 2001; Madsen et al., 2017). Indeed, the whole brain energy metabolism is correlated with levels of consciousness (Stender et al., 2015). However, the global cerebral metabolic rate of glucose (CMRglc) is not accessible using static \(^{18}\)F-FDG imaging due to the lack of an unaffected reference region. The gold standard for measuring CMRglc requires an arterial input function (AIF) and dynamic \(^{18}\)F-FDG with assessment of individual rate constants.

A Gjedde-Patlab plot with AIF and tissue time-activity curve utilizes the irreversible brain uptake of \(^{18}\)F-FDG \(\text{in-vivo}\) to estimate the unidirectional uptake rate constant \(K_t\) as the slope when the graph becomes linear after a sufficiently long time-period, \(t^*\) (Patlak et al., 1983; Gjedde, 1982). Several non-invasive methods using different population-based parameters have been proposed but they may be sus-

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https://doi.org/10.1016/j.neuroimage.2022.119079.
Received 27 October 2021; Received in revised form 16 February 2022; Accepted 7 March 2022
Available online 9 March 2022.
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ceptible to bias in case of cerebral disease. It must be stressed that all [18F]FDG methods for CMRglc are dependent on knowledge of the lumped constant (LC), which corrects for the differences between glucose and FDG in respect to transport, phosphorylation etc. and as LC is a population-based constant, bias may be introduced in case of disease or treatment modifying LC. A remarkable stable LC is, however, reported even during starvation that reduced the cerebral glucose consumption (Buschitzzzo et al., 2018).

The AIF is traditionally obtained through an arterial catheter, which is painful, considerably complicates the experimental set-up, and is not feasible in clinical routine. Obtaining an image derived arterial input function (IDIF) from cranial arteries requires correction for partial volume effects due to the small diameters (Sari et al., 2018) while larger intrathoracic arteries can be used uncorrected as is the case for cardiac perfusion studies (Endo et al., 1987). Activity measurements in large central arteries are known to exhibit an earlier, higher and narrower peak as compared to measurements in peripheral arteries. But the area-under-the-curve (AUC) is identical, which is also known from Sapirsteins bolus fractional principle (Sapirstein, 1956). The linear part of the Gjedde-Patlak plot initiates at $t^*$, thus estimations are unaffected by the shape of the input function before $t^*$, and brain measurements before $t^*$ can be omitted. Hence, from injection time to $t^*$, the initial part of the input function can be obtained from the aorta. After the brain scan, an acquisition of the aorta allows for interpolation of the input function during the brain scan. We aim to evaluate if this non-invasive three part dynamic PET recording with IDIF from the aorta can replace arterial cannulation to quantify cerebral glucose metabolic rate (CMRglc) by using a Gjedde-Patlak plot.

2. Method

2.1. Subjects

Healthy subjects were recruited at the Department of Clinical Physiology and Nuclear Medicine, Copenhagen University Hospital Bispebjerg, Denmark during the fall 2020. The study was approved by the Danish National Committee of Health Research Ethics (H-20026602) and was conducted according to the Declaration of Helsinki II. Written informed consent was obtained from all participants. Data was handled according to the regulations by the Danish Data Protection Agency.

Included were adult subjects with no prior history of cerebral disease or diabetes.

2.2. [18F]FDG PET/CT

All scans were obtained on a Discovery MI PET/CT (GE Healthcare, Chicago, United States).

The examinations were performed in the afternoon after at least four hours fasting. 200 MBq of [18F]FDG were injected manually as a short bolus of less than 5 s in the median cubital vein simultaneous with initiation of a three-part dynamic PET consisting of a 15 min-recording of the heart (frame durations 18 × 5 s, 9 × 10 s, 8 × 15 s, 10 × 30 s, 5 × 60 s), a 40 min-recording of the brain (8 × 5 min) and a 2 min-recording of the heart (1 × 2 min).

An initial “low dose” CTs of the aorta and the brain were performed and used for attenuation correction of the PET images, and Q.Clear, a “Bayesian penalized likelihood” algorithm (GE Healthcare, Chicago, United States), was used for tomographic reconstruction with a $\beta$-value of 100. Immediately before the scanning procedure, plasma glucose was measured from a capillary sample by a bedside Accu-Chek® Inform II system (Roche Diagnostics, Indianapolis, USA), calibrated to provide results as plasma values.

2.3. Arterial input function (AIF)

An arterial cannulation was placed either in the radial or the brachial artery preceded by 2 mL Lidocaine (10 mg/mL). Arterial blood was sampled throughout the scan. During the initial fifteen minutes, an on-line automatic blood sampling system (Allog ABSS, Stockholm, Sweden) was set to draw 7 mL/min. Annihilation sampling was done at 1 Hz. Data were corrected for decay and dead time before used for analysis. Manual blood samples were drawn at 2.5, 5.0, 7.5, 12.5, 15.0 min (for quality assurance) and hereafter every five minutes. Blood samples were obtained in lithium heparin coated test tubes. Samples (2–400 μL) were acquired before and after centrifugation at 3.000 RPM/1490 RCF for ten minutes (Universal 32, Hettich, Tutlingen, Germany) to separate plasma. Whole blood and plasma activity were measured by an automatic gamma counter (Hidex, Turku, Finland). The median of the plasma-whole-blood-ratio (PBR) from all samples was used as a constant for further IDIF and AIF analyses to reduce noise. The final AIF was constructed by fitting the ABSS values ($t_{15}$-$t_{15\text{ min}}$) and the later arterial samples ($t_{15\text{ min}}$-$t_{\text{end of scan}}$) to a triexponential function after the peak using PMOD 3.304 software (PMOD Technologies, Zurich, Switzerland).

2.4. Image derived input function (IDIF)

The PET scans of the aorta were loaded into the PMOD software. For delineating the aortic volume of interest (VOI), the dynamic frames from 4:20 to 15:00 minutes were summed and the resulting summed image and the late aortic scan were smoothed with a Gaussian kernel ($9$ mm $9$ mm $9$ mm). An ellipsoid VOI was manually drawn in the lumen of the descending aorta on the summed image in each patient (Median of the volume [range] of the VOI: $2,1 cm^3$ $[0,8 cm^3-6,9 cm^3]$) and median of the semi-axes (a,b,c) [range]: $(0.5 cm$ $[0.3 cm: 0.7 cm], 0.5 cm$ $[0.3 cm: 0.7 cm], 2.1 cm$ $[0.8 cm: 6.9 cm]$). Attempts of a VOI in the aortic arch resulted in less robust measures and were abandoned. The VOI was made as large as possible without interfering with the aortic wall in any frame. The VOI was copied to the late frame of the heart after visual check for movement artifacts. Whole blood activity concentration was extracted from the dynamic unsmoothed images using the aorta VOI. Obtained values were multiplied with the median PBR to estimate the plasma values and a triexponential model after the peak weighted according to frame duration was used for fitting the input function using PMOD. In this way, we estimated the missing plasma values for $T_{15 \text{ min}}$ – $T_{\text{end of scan}}$. Fits with linear interpolation and other models were also evaluated but resulted in significantly poorer goodness of fits.

2.5. Tissue activity curve (TAC)

The Tissue Activity Curve (TAC) was obtained by use of PMOD Neuro Tool's workflow for PET-only studies. VOIs were gained by Automatic Brain Regions by Probabilistic Atlas (Hammers-N30R83), using normalization to FDG control. Outlining of the regions included sulci deformations and masking of tissue. To reduce the number of regions, an average of right and left hemisphere was calculated for superior frontal cortex, insula, hippocampus and cerebellum.

2.6. Calculation of CMRglc

CMRglc was calculated from a Gjedde-Patlak plot using respectively the IDIF (CMRglc_{IDIF}) and AIF (CMRglc_{AIF}) in the PMOD software as input functions and the brain activity concentration curves as TAC with plasma glucose concentration as measured, a lumped constant of 0.65, and blood volume, $V_b$ fixed to 0.05.

2.7. Statistical analyses

Paired student’s T-test was used to compare area under the curve of the fitted input functions (AUC). The predictive value of CMRglc_{IDIF}...
was analyzed by a linear mixed model with CMRglc_AIF set as dependent value, CMRglc_IDIF as fixed whereas subjects and regions were set as random effects. All the extracted regions were used in the analysis of the predictive value to gain enough data points. For the four chosen regions, CMRglc_IDIF and CMRglc_AIF were compared with paired t-test and Bland-Altman statistics with calculation of limits of agreement. The mean of the relative differences was calculated from the individual (CMRglc_IDIF − CMRglc_AIF) / CMRglc_AIF Analyses were performed in R statistical software (R Core Team, 2017; R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org).

3. Results

Six participants (age 30–68 years, 3 women) were recruited. Arterial cannulation was performed in the radial (n = 4) or in the brachial artery (n = 2). The arterial sampling line clotted after approximately 10 min in one patient but manual samples were achievable afterwards. A total of 85 arterial blood samples from all subjects for PBR were obtained successfully with a median PBR of 1.0877 (1Qu:4Qu:1.0708:1.1058). The measured PBR values did not change over time and no significant differences between subjects were observed.

As expected, the activity peak in aorta was earlier, higher and narrower than the activity peak measured by arterial cannulation. Note that a large part of the difference is due to dispersion by external tubing. The values obtained by both methods were comparable with a slight difference in the fitting of the triexponential curves (Figs. 1 and 2), and AUC were not significantly different with median [range] of relative differences of -2.9% [-8.1%: 6.1%] (p = 0.43). Despite suboptimal visual fitting (Fig. 2) of the measured arterial values using a triexponential fitting, the median [range] of the relative difference between the AUC with and without triexponential fitting were only 1.2%; range [-2.3%: 6.8%], p = 0.33). Further, the above mentioned difference of -2.9% between AIF and IDIF AUC using triexponential fittings were in the same order of magnitude as comparing IDIF AUC to AUC from the measured arterial values without the exponential fitting (0.31% [-6.3%: 4.1%], p = 0.99).

The mixed model analysis of the predictive value of CMRglc_IDIF resulted in a slope of 1.00 ± 0.08, with an intercept of 1.00 ± 1.39 with a random effect of subject ID at 0.85 ± 0.92, thereby demonstrating a strong linear relationship between CMRglc_AIF and CMRglc_IDIF with only small differences between subjects (Fig. 3). Subject number five had slightly higher values for IDIF as compared to AIF propagating into increasing difference between IDIF and AIF with increasing CMRglc (Figs. 3 and 4). The difference, however, was below 8.5%. The low variation, no significant differences, and excellent agreement were confirmed in a subanalysis of the four sub regions (Table 1) Fig. 4. shows Bland-Altman plot from all the regions (Hammers-N30R83 atlas).

4. Discussion

We present data related to IDIF from the aorta before and after a dynamic [18F]FDG brain scan for non-invasive CMRglc measurements. We found excellent agreement between CMRglc measurements using an IDIF from aorta and an invasive AIF with a slope of the linear relationship of 1.00 ± 0.08, narrow limits of agreement, and a mean deviation of 2.2–3.8%. Test-retest differences of [18F]FDG brain scans using invasive arterial cannulation of 4.3% have been reported (Schmidt et al., 1996). Although scanner resolution has improved since 1996, we anticipate that noise originating from blood measurements is unchanged.

Previous studies using partial volume correction derived from simultaneous MRI in a PET/MR hybrid system have reported errors of 5.8% (Shiyam Sundar et al., 2020; Sundar et al., 2019), while extraction of an IDIF from carotid arteries scaled to manual samples resulted in less optimal results in two of nine subjects (Huisman et al., 2012). The presented method show high agreement compared to IDIF methods with partial volume correction (Croteau et al., 2010; Zhou et al., 2011).

The strength of the method is the lack of complicated partial volume corrections that may be scanner-specific or need for scaling to a blood sample. This makes the procedure simple for routine clinical studies of patients with presumed global changes of CMRglc. The present method can therefore be used in all standard PET systems even with narrow field-of-view. The lack of blood measurements obviates the need for cross calibration of scanners to online sampler reducing the risk of bias and measurement-related noise as all measurements are performed in the same system. We propose that the method is especially useful to evaluate treatment effects that presumably affects the entire brain [18F]FDG consumption.

Limitations of the study include the limited sample size of only six healthy subjects. However, as an IDIF from aorta is a validated approach for heart studies, the present comparison only evaluates the triexponential...
Fig. 2. Showing the fitted IDIF (black) and AIF (red) curves along with the datapoints for the blood samples (circles) and the aortic scan (triangles).

Table 1
Mean values and agreement of CMRglc ($\mu$mol 100 g$^{-1}$ min$^{-1}$) along with the mean of the relative difference (%) derived by AIF and IDIF in SFC, insula, hippocampus and cerebellum.

| Region   | $\text{MRCglc}_{\text{AIF}} \pm \text{SD}$ | $\text{MRCglc}_{\text{IDIF}} \pm \text{SD}$ | $p$       | Mean Difference [95% CI] | Lower LOA [95% CI] | Upper LOA [95% CI] | Mean of the relative difference (%) [Range] |
|----------|------------------------------------------|------------------------------------------|----------|------------------------|-------------------|-------------------|---------------------------------------------|
| SFC      | 30.9 ± 4.0                               | 30.4 ± 3.3                               | 0.31     | -1.6                   | [-0.6:1.6]        | [0.5:4.6]         | 2.5 [0.5:6.8]                               |
| Insula   | 25.8 ± 2.5                               | 25.4 ± 2.2                               | 0.30     | -1.4                   | [-0.5:1.4]        | [0.5:4.0]         | 2.2 [0.0:7.3]                               |
| Hippocampus | 17.3 ± 1.4                            | 16.9 ± 1.2                               | 0.24     | -1.1                   | [-0.4:1.3]        | [0.5:3.5]         | 2.0 [0.8:4.4]                               |
| Cerebellum | 23.9 ± 2.5                            | 23.4 ± 1.9                               | 0.24     | -1.4                   | [-0.5:1.6]        | [0.6:4.4]         | 2.5 [0.8:4.4]                               |

CMRglc: Cerebral metabolic rate of glucose, AIF: arterial input function, IDIF: image derived input function, SFC: Superior frontal cortex, CI: confidence interval, LOA: limits of agreement. The mean relative difference for all four regions was 2.9%.

Fig. 3. Scatter plot of CMRglcAIF and CMRglcIDIF ($\mu$mol 100 g$^{-1}$ min$^{-1}$) in the different brain regions (Hammers-N30R83 atlas) for each subject. Each subject with his/her own mark. The solid line is the regression line from the mixed model with slope of 1.00 ± 0.08, with an intercept of 1.00 ± 1.39.

Fig. 4. Bland-Altman plot presenting the agreement of CMRglc ($\mu$mol 100 g$^{-1}$ min$^{-1}$) in all regions (Hammers-N30R83 atlas). Difference= 0.5 $\mu$mol 100 g$^{-1}$ min$^{-1}$, LOA$_{lower}$= -1.3 $\mu$mol 100 g$^{-1}$ min$^{-1}$ and LOA$_{upper}$= 2.2 $\mu$mol 100 g$^{-1}$ min$^{-1}$.

Tential interpolation between the IDIF obtained before and after the brain scan. No pathological conditions are expected to influence the ability to interpolate blood data, and we recommend no restrictions for applying the method in diabetes or medical conditions that could interfere with the shape of the input function. Movement artifacts could influence the VOI delineation and attenuation corrections and care must be taken in patients who cannot lie still. No movement correction was done in
the present study but visual inspection of the aorta VOI was performed. Especially the late frame is critical for the definition of the tail and care must be taken in checking the VOI position. The initial part of the scan with very short frames is difficult to correct for movements due to the higher noise levels, and as the study evaluates the input function, we do not believe that movement correction would change the results significantly. Movement correction of the brain scan can preferably be applied in studies of brain metabolism. The manual drawing of the VOI in aorta may be subject to error and interrater variation but the noise from VOI drawing should be compared to the noise from blood measurements. Using a two-min recording for the late heart frame results in low counts, and we recommend extending the frame length to four-min to diminish noise. The IDIF is multiplied by a population-based PBR and individual changes in the contribution of activity from plasma and erythrocytes may bias the IDIF, e.g. in case of anemia. Changes in a plasma-breadth ratio close to 1 will, however, only change the CMRglc slightly but care must be taken if changes in hematocrit in patients or during treatment are expected. In the present study, the whole blood measurements were multiplied to the median PBR reducing noise from the blood measurements, and the measured population-based PBR was in line with previous reports (Naganawa et al., 2020). We recommend that PBR is measured if the stability of the measure is in doubt.

We suggest that the present method can be useful for research purposes in patients with global brain affection of any kind.

In conclusion, we found excellent agreement of a non-invasive 1 h method for measuring the cerebral metabolic rate of glucose compared to the reference standard. The method relies on three-part dynamic (18)F-FDG PET imaging using IDIF from aorta to create a Gjedde-Patkal plot and allows for non-invasive detection of global cerebral metabolic changes. The method is useful with all scanner systems and does not require arterial blood samples and partial volume correction.

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