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Short Communication

Correction of Positron Emission Tomography Data for Cerebral Atrophy

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Summary: Because positron emission tomography (PET) provides measurements per unit volume of intracranial contents, these measurements may be affected by the inclusion of metabolically inactive CSF spaces in the volume in which they are made. Thus, PET measurements of CBF and metabolism may be artifactually lowered in normal aging and dementia, which are both associated with significant brain atrophy. We describe a method to correct global PET data, averaged over several tomographic slices, for cerebral atrophy by using measurements of CSF space volume obtained with quantitative x-ray computed tomography. The importance of making such a correction is demonstrated using PET measurements of CBF and oxygen metabolism obtained in normal young, normal elderly, and demented subjects.
Key Words: Alzheimer's disease—Dementia—Normal aging—Positron emission tomography—X-ray computed tomography.

Since the pioneering work of Kety, Schmidt, and colleagues (Kety and Schmidt, 1948; Freyhan et al., 1951), the effects of normal aging and dementia on cerebral hemodynamics and metabolism have been subjects of ongoing investigation. A variety of techniques have been used to study these issues, including the classic Kety–Schmidt method, intracarotid injection of radiotracers, ^{133}Xe inhalation, and, more recently, positron emission tomography (PET). Prior to the use of PET, declines in both CBF and metabolism in dementia were demonstrated (Dastur, 1985). Findings in normal aging were less consistent, however, with several, but not all, studies showing no age-related changes [for reviews, see Sokoloff (1979), London (1984), Creasey and Rapoport (1985), Dastur (1985)]. Different selection criteria for the aged subjects may account for some of the variability in these studies (London, 1984). More recent studies of dementia using PET similarly have demonstrated declines in CBF, $CMRO_2$ (Frackowiak et al., 1981), and CMRglu (Benson et al., 1983; de Leon et al., 1983; Foster et al., 1984). However, PET studies have produced conflicting results in normal aging. Some investigators have found age-related declines in CBF, $CMRO_2$ (Frackowiak et al., 1980; Lenzi et al., 1981; Frackowiak and Gibbs, 1983; Pantano et al., 1984), and CMRglu (Kuhl et al., 1982), while others have found CMRglu to be age invariant (de Leon et al., 1983; Duara et al., 1984).

Both normal aging and senile dementia of the Alzheimer type (SDAT) are associated with brain atrophy (Gado et al., 1982; Zatz et al., 1982; Damasio et al., 1983; de Leon et al., 1983; Schwartz et al., 1985). Measurements of CBF, $CMRO_2$, and CMRglu using earlier nontomographic methods, such as the Kety–Schmidt technique (1948), are not affected by brain atrophy because these methods record data only per unit of extant tissue. Tomographic techniques such as PET, on the other hand, provide physiologic measurements per unit volume of intracranial contents. Thus, global PET

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Abbreviations used: CBV, cerebral blood volume; CDR, clinical dementia rating; CT, computed tomography; PET, positron emission tomography; SDAT, senile dementia of the Alzheimer type; $(V+S)\%$, percentage of intracranial volume occupied by ventricles and sulci.

data, averaged over one or more tomographic slices, will be affected by the inclusion of metabolically inactive CSF spaces in the volume over which the PET measurement is averaged. Data equivalent to those given by the Kety–Schmidt technique can be obtained only by explicitly correcting PET measurements for the presence of CSF spaces, or by selecting regions of interest such that partial volume averaging with ventricular or sulcal spaces is avoided, an approach difficult to implement because of the limited spatial resolution of PET. Given this problem, it is difficult to determine whether changes observed in PET measurements in normal aging and dementia are due to changes in brain hemodynamics and metabolism, brain atrophy, or a combination of the two. In this study, we describe a strategy to correct global PET measurements for the effects of cerebral atrophy by integrating data from both quantitative computed tomography (CT) scans and PET scans. We illustrate its application to data obtained in three groups: normal young, normal aged, and SDAT subjects. A preliminary report of this approach has previously appeared (Herscovitch et al., 1983*b*).

MATERIALS AND METHODS

Three groups of subjects were studied: 10 normal young subjects [mean age 27.5 ± 3.6 (SD) years, range 22–34 years], 8 normal aged subjects (mean age 72.8 ± 5.2 years, range 68–84 years), and 6 SDAT subjects (mean age 75.3 ± 2.6 years, range 71–79 years). The young group consisted of healthy volunteers who were without known neurological, psychiatric, or chronic medical diseases. Normal aged and SDAT subjects were enrolled in the Memory and Aging Project at Washington University Medical Center (Berg et al., 1982). Normal aged subjects were without evidence of neurological, psychiatric, or chronic medical diseases by history, physical examination, laboratory studies, and head CT except for the presence of atrophy. In addition, they all had a score of 0 (healthy) on the clinical dementia rating (CDR) scale (Berg et al., 1982; Hughes et al., 1982). All SDAT subjects exhibited gradual onset and progression of global intellectual deterioration for ≥6 months and had CDR scores of 1 (mild dementia). Other causes of the dementia syndrome were specifically excluded by history, physical examination, laboratory studies, and head CT. The SDAT patients were also without evidence of other neurological, psychiatric, or chronic medical diseases.

PET was performed using the PETT VI system (Ter-Pogossian et al., 1982; Yamamoto et al., 1982). This machine collects seven contiguous tomographic slices with a center-to-center separation of 14.4 mm and a transverse resolution of 12.4–14.0 mm. Each subject received a single intravenous bolus injection of $H_2{}^{15}O$, and briefly inhaled air containing trace amounts of $C^{15}O$ and $O^{15}O$. Scan data obtained following the administration of each tracer were used to calculate CBF, cerebral blood volume (CBV), and $CMRO_2$. The mathematical models that underlie these measurements and details of their implementation with the PETT VI system have been previously described (Grubb et al., 1978; Herscovitch et al., 1983*a*; Raichle et al., 1983; Mintun et al., 1984). At the time of each study, a lateral skull radiograph was obtained with the center of each PET slice marked by a radiopaque wire (Fox et al., 1985). This record of the PET slices in relation to the bony landmarks of the skull was subsequently used to obtain CT slices encompassing the same brain regions. A tomographic transmission scan using a ring source of activity containing $^{68}Ge/^{68}Ga$ was performed in each subject to determine the attenuation characteristics of the head. All scans were done with the patient in the resting state; room lights were dimmed, and ambient noise was primarily from cooling fans for the electronic equipment. Oxygen content and carbon dioxide tension were measured on samples of arterial blood drawn from an indwelling arterial cannula during each PET study.

Global average values for each subject's CBF, $CMRO_2$, and CBV were obtained from four contiguous supratentorial PET slices. The intracranial dimensions were defined by a threshold routine applied to each subject's attenuation scan. The outer table of the skull was determined by removing from the periphery of the attenuation image all pixels having values <80% of the maximum photon attenuation value for that slice. An additional two pixels (5.4 mm) were circumferentially removed from the border of the 80% thresholded attenuation image to define the inner table. This method has previously been shown to correlate with intracranial dimensions in normal subjects (Fox et al., 1985). The intracranial dimensions thus defined were then used as a template for that subject's CBF, $CMRO_2$, and CBV images. Global values were then calculated by averaging data from the four PET slices. These global values were thus derived from an intracranial volume that contains both metabolically active brain tissue and metabolically inactive CSF spaces.

CT scans were performed on Siemans Somatom II scanners. Contiguous CT slices 8 mm thick were obtained. A CT-generated digital radiogram (Topogram) provided a lateral view of the skull in the CT gantry. This was used in conjunction with the lateral radiograph obtained at the time of PET, to angulate the CT scanner gantry and obtain CT slices parallel to and encompassing the same brain regions as the PET slices. Volumetric measurements of CSF spaces (ventricles plus sulci) were generated from the seven adjacent supratentorial slices (total thickness 56 mm) corresponding to the four PET slices (total thickness 57.6 mm). The volumes that were studied included the lateral and third ventricles and the central white matter. They excluded the highest sections, which might contain partial volume artifacts caused by the curve of the calvaria, and the lowest ones, containing the posterior fossa as well as artifacts caused by the base of the skull and air spaces (Gado et al., 1982). The volume of ventricles and sulci was expressed as a percentage of intracranial volume, i.e., $(V+S)\%$, by calculating the number of pixels of CSF density and dividing by the total number of intracranial pixels in the slices (Gado et al., 1982). The $(V+S)\%$ measurements were used to individually correct PET measurements for variability in amount of brain atrophy (see below). Individual measurements of $(V+S)\%$ were obtained for each normal aged subject and each SDAT subject. The young normal subjects did not receive individual quantitative CT examinations. Instead, we used the average value of $(V+S)\%$ determined by the quantitative CT study of an equal number (n = 10) of

age-matched [mean age 28.6 ± 2.3 (SD) years, range 25–33 years] patients who had received CT scans as part of a clinical evaluation for various medical complaints [headache (six), depression (two), facial trauma (one), and parasthesias (one)]. They were selected from sequential CT examinations at our institution on the basis of age, a normal neurological exam, and a CT scan reading that, excluding assessment of CSF spaces, was normal.

To accurately compare the CBF, $CMRO_2$, and CBV per unit brain tissue in the normal young, normal aged, and SDAT states, it is necessary to correct the global PET values calculated as described above for the amount of cerebral atrophy encountered in each subject (Herscovitch et al., 1983*b*). We accomplished this by dividing the calculated global values of CBF, $CMRO_2$, and CBV for each subject by the fraction of their intracranial volume actually occupied by brain tissue. This fraction is equal to $1 - 0.01 \times (V+S)\%$ for each subject.

Comparisons among the three groups were tested for significance with analysis of variance and the Neuman–Keuls multiple-range test using an experimentwise α level of 0.05. Because seven separate measurements [age, PCO_2, O_2 content, $(V+S)\%$, CBF, $CMRO_2$, CBV] were made, an α level of 0.0071 was used for each of the seven analyses to compensate for the effect of multiple comparisons. All grouped data are expressed as the mean and 1 SD.

RESULTS

The normal aged group and the SDAT group did not differ significantly in age, whereas both differed significantly from the young normals. None of the groups differed significantly from one another in arterial PCO_2 or in arterial O_2 content. Significant differences existed among all three groups in the volume of CSF spaces (Table 1).

Mean uncorrected and corrected global values for CBF, $CMRO_2$, and CBV appear in Table 2. The uncorrected values show that SDAT subjects have a significantly lower global CBF than the normal young or normal aged subjects and a significantly lower $CMRO_2$ than normal young subjects. Normal young subjects and normal aged subjects showed no significant differences in any of the three PET measurements. When these data are corrected for individual variations in $(V+S)\%$, the depression in CBF in SDAT subjects was less marked in comparison with normal subjects, and no difference was observed among the three groups in $CMRO_2$.

TABLE 1. *Volume of supratentorial intracranial cavity occupied by ventricules and sulci*

Group	$(V+S)\%$[a]
Normal young subjects (n = 10)	4.67 ± 0.97
Normal aged subjects (n = 8)	10.57 ± 3.38
SDAT subjects (n = 6)	18.98 ± 5.76

Values are means ± SD. $(V+S)\%$, percentage of intracranial volume occupied by ventricles and sulci; SDAT, senile dementia of the Alzheimer type.

[a] SDAT subjects > normal aged subjects > normal young subjects. All inequalities $p < 0.005$.

TABLE 2. *Effects of correction for CSF spaces on global positron emission tomography measurements in aging and mild senile dementia of the Alzheimer type (SDAT)*

Measurement	Normal young subjects (n = 10)	Normal aged subjects (n = 8)	SDAT subjects (n = 6)
CBF (ml/min/100 g)			
Uncorrected	49.6 ± 6.3[a]	46.0 ± 7.4[a]	27.4 ± 4.3
Corrected	52.2 ± 6.7[a]	51.9 ± 8.9[a]	34.0 ± 4.2
$CMRO_2$ (ml/min/100 g)			
Uncorrected	2.68 ± 0.41[a]	2.17 ± 0.44	1.75 ± 0.23
Corrected	2.81 ± 0.43	2.44 ± 0.53	2.17 ± 0.32
CBV (ml/100 g)			
Uncorrected	5.14 ± 0.85	5.12 ± 1.13	3.88 ± 0.27
Corrected	5.41 ± 0.88	5.73 ± 1.24	4.83 ± 0.41

Values are means ± SD. CBV, cerebral blood volume.

[a] Significantly different from SDAT.

DISCUSSION

PET differs from earlier nontomographic techniques of measuring CBF and metabolism, such as the Kety–Schmidt method, in that it provides measurements per unit of volume of intracranial contents. Thus, metabolically inactive CSF spaces may be included in the volume in which the PET measurement is made. As observed in this study, and as has been described by others (Gado et al., 1982; Zatz et al., 1982; Damasio et al., 1983; de Leon et al., 1983; Schwartz et al., 1985), there is an increase in the size of the CSF spaces in normal aging and, to a greater extent, in SDAT. This could result in an artifactual lowering of global PET measurements of CBF and metabolism in aging and SDAT.

We have described a method to correct such global PET measurements for the effect of cerebral atrophy. When this strategy was applied to global PET data obtained in normal young, normal aged, and SDAT subjects, the corrected data led to observations different from those obtained from the uncorrected measurements. Thus, corrected CBF in SDAT patients was less depressed in comparison with normal subjects than was the uncorrected CBF. The decrease that was seen in uncorrected $CMRO_2$ in SDAT did not reach statistical significance when the data were corrected for cerebral atrophy. These findings demonstrate the importance of correcting global PET measurements for cerebral atrophy, especially in patient groups in which the size of the CSF spaces may vary. They indicate that a component of the decline in global CBF and metabolism observed in PET studies of

normal aging and dementia may be due to a lack of correction for cerebral atrophy. Certain investigators who measured both CBF and $CMRO_2$ in aging, however, have noted a steeper decline in one than the other, that is, either in $CMRO_2$ (Pantano et al., 1984) or in CBF (Frackowiak and Gibbs, 1983), suggesting a physiological process in addition to any methodological effects.

The finding that corrected $CMRO_2$ in the SDAT subjects was not significantly decreased should be interpreted with caution. First, our subjects had only mild dementia (CDR = 1), whereas other studies included more severely affected patients (Frackowiak et al., 1981). Second, the relatively small patient sample reduced our ability to detect statistically significant differences in the measurements made, especially with the adjustment of level of statistical significance for multiple comparisons.

The strategy we used to correct global PET data for cerebral atrophy requires that both the PET and CSF space measurements be obtained from the same intracranial volume. It is not necessary, however, that there be a one-to-one correspondence between individual PET and CT slices, as these, in general, will have different slice thicknesses. We recorded the levels of our PET slices in relation to the bony landmarks of the skull on a lateral skull radiograph (Fox et al., 1985). A similar lateral digital radiogram (Topogram) obtained with the subject in the CT gantry permitted selection of the CT angle and levels so that CT slices could be obtained to encompass the same intracranial volume as the PET slices. This procedure was performed in our normal aged and SDAT subjects, but not in the young normals. In these latter subjects, the CT and PET slices encompassed equivalent intracranial levels (i.e., including the lateral ventricles and central white matter), but differed somewhat in angulation. However, studies in which CT measurements were performed at different angles in the same subjects have shown that the resulting variation in $(V+S)\%$ is $<7\%$ of the baseline value (M. Gado, unpublished results).

We used a semiautomated technique to determine the size of the CSF spaces in relation to the intracranial volume in contiguous CT slices (Gado et al., 1982). Certain factors may limit the accuracy of this technique in determining CT pixels corresponding to CSF. These include the partial volume effect (Goodenough et al., 1982), resulting in some pixels having attenuation intermediate between CSF and parenchyma; beam-hardening artifacts (Brooks and DiChiro, 1976), increasing CT numbers near bone; and the selection of the CT density cutoff level used to identify pixels of CSF density. In spite of these potential problems, the technique has been validated in cadavers in which CT measurements were found to be highly correlated with direct, independent determinations of brain and CSF volumes (M. Gado et al., unpublished results). Another potential difficulty is the occurrence, in some elderly and demented subjects, of areas of low white matter attenuation (Mori et al., 1980; Goto et al., 1981), which could erroneously be included in the measurement of CSF volume. None of our subjects, however, had such white matter lucencies. Finally, we note that our strategy for correcting global PET measurements for cerebral atrophy is compatible with other methods for estimating CSF space volume, using either CT (Zatz et al., 1982; Albert et al., 1984; Schwartz et al., 1985) or magnetic resonance images, provided the PET and anatomic measurements are obtained from equivalent intracranial volumes.

A major strength of PET is its ability to provide measurements on a regional basis. Such regional measurements may provide more insight into alterations in CBF and metabolism associated with aging or dementia than global averages. In addition, measurements obtained from multiple representative brain regions can be averaged to obtain an estimate of global values (Frackowiak et al., 1981; Pantano et al., 1984). Individual regional measurements may also be artifactually reduced, however, by contamination with CSF spaces, for example, by partial volume averaging with a nearby sulcus or ventricle, or when part of the region itself consists of the CSF space. It should be possible to develop a strategy to correct regional PET measurements for these effects, using x-ray CT or magnetic resonance images obtained in the same plane as the PET slices.

In summary, we have described a method to correct global values of PET measurements for the percentage of the intracranial volume occupied by CSF. Such a correction is particularly required when PET is used to study conditions associated with significant degrees of cerebral atrophy, such as normal aging and SDAT.

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