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Changes in human cerebral blood flow and myocardial blood flow during mental stress measured by dual positron emission tomography

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Mental stress causes a substantial sympathetic response, thus increasing myocardial blood flow (MBF). However, the effects of mental stress on global CBF have not been elucidated. In this study, changes in CBF and MBF in relation to mental stress were measured by a dual positron emission tomography system that can measure CBF and MBF simultaneously. CBF and MBF were measured in 10 healthy men with O-15 labeled water at rest (baseline) and during the performance of a mental task that required subtraction of 7s serially from a four-digit number. Baseline global CBF and values obtained during the mental activity were 0.42 ± 0.05 and 0.45 ± 0.06 ml/ml/min (mean ± SD), respectively. Baseline MBF and values obtained during mental activity were 0.61 ± 0.12 and 1.09 ± 0.58 ml/ml/min, respectively. Percent changes in CBF and MBF during mental stress were 6 ± 11% and 78 ± 73%, respectively. No significant difference was observed in P_aCO_2 level between the mental stress and baseline conditions. MBF, blood pressure, heart rate, and plasma concentrations of adrenaline and noradrenaline increased significantly during mental stress. Sympathetic stimulation is reported to cause cerebral vasoconstriction and reduce CBF in animals. Although such a sympathetic response was observed in relation to mental stress, no significant change in CBF was observed in our subjects.

Key words: mental stress, CBF, MBF, human, PET

INTRODUCTION

Mental stress causes a substantial sympathetic response characterized by increases in blood pressure, heart rate, and plasma catecholamine levels.[1–4] Mental stress also induces coronary artery vasodilatation[5,6] and an increase in myocardial blood flow (MBF).[7] Therefore, mental stress can be used for estimation of coronary flow reserve in patients with coronary artery disease.[7] In such patients, mental stress experienced in daily life can cause myocardial ischemia evidenced by ischemic changes on the electrocardiogram[8] and by left ventricular dysfunction.[1,9]

The effects of mental stress on cerebral blood flow (CBF) have not been elucidated, however. Only a few reports exist concerning the effects of mental stress on CBF. One report shows an increase in global CBF measured with ^{133}Xe during the performance of a mental task.[10] Another report shows no change in global CBF measured with ^{133}Xe in relation to mental stress verified by increased plasma concentrations of adrenaline.[11] Mental stress causes a sympathetic response, and the sympathetic innervation of the intracranial arteries contributes to the regulation of cerebral perfusion.[12,13] Sympathetic stimulation has been reported to reduce CBF in cats[14] and dogs,[15] whereas no change in CBF during sympathetic stimulation has been observed in baboons.[16] Parasympathetic stimulation has been reported to increase CBF in cats.[17] An increase in CBF after stellate ganglion block has also been observed in humans by means of single photon emission tomography with ^{99m}Tc-labeled hexamethylpropyleneamineoxime.[18]

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We have developed a dual positron emission tomography (dual-PET) system that allows simultaneous study of human brain and heart measurement of both CBF and MBF.[19] In the present study, changes in CBF and MBF in relation to mental stress were investigated with this dual-PET system.

METHODS

Subjects

Ten healthy right-handed men (20–28 years of age) were recruited and gave written informed consent to participate in the study. The subjects were judged to be healthy based on medical history, physical examination, blood screening analysis, and magnetic resonance imaging of the brain. The study was approved by the Ethics Committee of the Akita Research Institute of Brain and Blood Vessels.

PET procedures

The Headtome-V dual-PET (Shimadzu Corp., Kyoto, Japan) used for all studies provides 47 sections with center-to-center distances of 3.125 mm.[20] The intrinsic spatial resolution was 4.0 mm in plane and 4.3 mm full width at half maximum (FWHM) axially. Reconstruction with a Butterworth filter resulted in a final in-plane resolution of approximately 8 mm FWHM.

The dual-PET system was used as previously described.[19] After 1-min continuous inhalation of $C^{15}O$ gas (approximately 5 GBq total supplied to the mouth), a 4-min static scan was obtained and three arterial blood samples were taken. $C^{15}O$ PET data from the heart were used to derive the arterial input function for calculation of MBF.[21] Following the transmission scan, $H_2{}^{15}O$ PET studies were performed at rest (baseline) and during the performance of a mental stress. The interval between the baseline and mental stress studies was at least 15 min. The order of the two $H_2{}^{15}O$ PET studies was randomized. The scanning protocol consisted of a 180-sec static scan of the brain and 360-sec dynamic scan of the heart following continuous intravenous infusion of $H_2{}^{15}O$ over 2 minutes. The dose of radioactivity was 1.2 to 1.5 GBq at the start of scanning. The arterial input function for calculation of CBF was obtained by continuous beta probe measurement of radioactivity in arterial whole blood taken from the radial artery. Dispersion and delay occurring in the beta detector system and in the internal-arterial line were corrected according to methods previously reported.[22,23] CBF images were calculated by the autoradiographic method.[19,24,25] MBF was calculated from the heart PET camera data[19] by use of the arterial input function derived from the left ventricular time-activity curve measured by the PET camera ring positioned over the heart.[21] Two arterial blood samples were taken, one at the beginning and one at the end of brain scanning, to measure arterial CO_2 gaseous pressure. Blood pressure and heart rate were monitored during each scan. Arterial plasma concentrations of adrenaline, noradrenaline, and dopamine during each scan were also measured. A head fixation system with individual molds for each subject was used to minimize head movement over the period of PET measurement.

The mental stress condition started 1 min before scanning and continued until the end of scanning. The mental stress protocol during PET scanning consisted of mental arithmetic, that is, the subtraction of serial 7s from a four-digit number as quickly and as accurately as possible.[1,2] The subjects were instructed to provide verbal responses.

Regions of interest

Regions of interest (ROIs) were drawn on all CBF images. Circular ROIs (16 mm in diameter) were defined for the pons, thalamus, and putamen, and elliptical ROIs (16 mm × 32 mm) were defined for the cerebellar cortex, centrum semiovale, and four neocortical regions representing the frontal, temporal, parietal, and occipital lobes. Each ROI was drawn in three adjacent sections, and data were pooled to obtain the average concentration of radioactivity for the whole volume of interest. An ROI for the contour of the whole cerebrum (without pons and cerebellum) was also drawn on all CBF images. The ROI for the contour of the left ventricular wall including the anterior and lateral walls was drawn on the heart images obtained from the $H_2{}^{15}O$ PET scan.

Anatomic standardization analysis

To detect the brain region showing neural activation due to the mental stress, anatomic standardization analysis was performed. All CBF images were transformed into the standard brain size and shape by linear and nonlinear

Table 1 P_aCO_2, P_aO_2, pH, blood pressure (BP), heart rate (HR) and heart rate-systolic pressure product (RPP) during $H_2{}^{15}O$ PET scanning

Condition	P_aCO_2 (mm Hg)	P_aO_2 (mm Hg)	pH	BP (Systole/Diastole) (mm Hg)	HR (beats/min)	RPP (mm Hg · beats/min)
Baseline	40.9 ± 2.3	98.6 ± 6.6	7.417 ± 0.015	126 ± 9/64 ± 6	63 ± 5	7906 ± 788
Mental stress	40.8 ± 2.0	105.1 ± 4.8‡	7.419 ± 0.020	137 ± 9†/72 ± 6*	74 ± 8*	10135 ± 1196*

Values are shown as mean ± SD

Significant differences from baseline values (paired t-test): *$p < 0.001$, †$p < 0.01$, ‡$p < 0.05$

Table 2 Plasma concentrations of adrenaline, noradrenaline, and dopamine during $H_2{}^{15}O$ PET scanning

	Adrenaline (ng/m*l*)	Noradrenaline (ng/m*l*)	Dopamine (ng/m*l*)
Baseline	0.046 ± 0.031	0.152 ± 0.068	0.049 ± 0.072
Mental stress	0.073 ± 0.031*	0.185 ± 0.062*	0.043 ± 0.066

Values are shown as mean ± SD
Significant differences from baseline values (paired t-test): *$p < 0.01$

Table 3 Baseline CBF and MBF and values during mental stress

	Baseline (ml/ml/min)	Mental stress (ml/ml/min)
CBF		
Pons	0.40 ± 0.07	0.44 ± 0.08
Cerebellum	0.59 ± 0.08	0.71 ± 0.11*
Thalamus	0.58 ± 0.06	0.66 ± 0.12
Putamen	0.63 ± 0.11	0.72 ± 0.16†
Frontal cortex	0.48 ± 0.05	0.51 ± 0.09
Temporal cortex	0.53 ± 0.08	0.57 ± 0.10
Occipital cortex	0.57 ± 0.09	0.56 ± 0.07
Parietal cortex	0.54 ± 0.08	0.61 ± 0.11
Centrum semiovale	0.21 ± 0.05	0.22 ± 0.06
Whole cerebrum	0.42 ± 0.05	0.45 ± 0.06
MBF	0.61 ± 0.12	1.09 ± 0.58†

Values are shown as mean ± SD.
Significant differences from baseline values (paired t-test): *$p < 0.01$, †$p < 0.05$

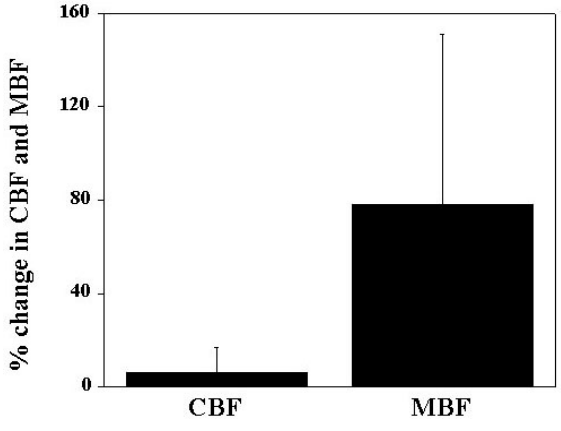

Fig. 1 Percent change in CBF of the whole cerebrum and MBF during mental stress activity. MBF is significantly increased during mental stress. No significant change is seen in CBF of the whole cerebrum.

parameters with a system (SPM99) for anatomic standardization.[26] After anatomic standardization, the brain images of all subjects had the same anatomic format. All images were globally normalized for pixel counts. From these standardized images, a three-dimensional t-map of the mental stress condition minus the baseline measurement was created on a pixel-by-pixel basis. Areas on this map showing a p-value of <0.001 with no correction were considered to be statistically significant. The extent threshold was set at 64 voxels (1 voxel: 2 × 2 × 2 mm).

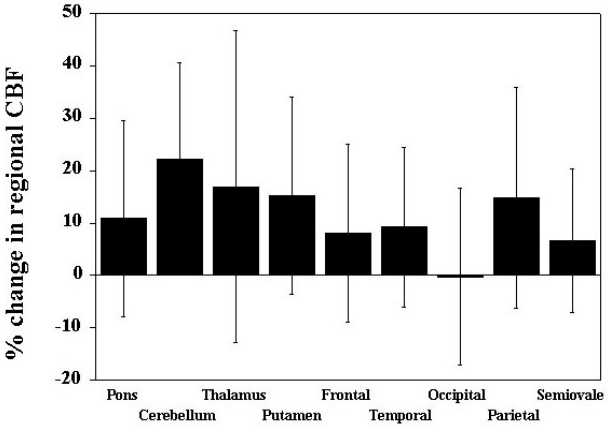

Fig. 2 Percent changes in regional CBF during mental stress. CBF in the cerebellum and putamen are significantly increased during mental stress activity.

RESULTS

P_aCO_2, P_aO_2, pH, blood pressure, heart rate, and heart rate-systolic pressure product (RPP) obtained during each $H_2{}^{15}O$ PET study are given in Table 1. Blood pressures were measured at the ankle in these studies, and are thus systematically greater value than pressures measured at the brachium. Blood pressure, heart rate, and RPP were significantly greater during the mental stress condition than at baseline ($p < 0.001$–0.01). No significant difference was observed in P_aCO_2 between the mental stress and baseline conditions, although P_aO_2 was significantly higher during the mental stress activity than at baseline measurement ($p < 0.05$). Hemoglobin concentration and hematocrit values were 14.8 ± 1.1 g/d*l* and 44.1 ± 3.4%, respectively (mean ± SD).

Plasma concentrations of adrenaline, noradrenaline, and dopamine during each $H_2{}^{15}O$ PET study are given in Table 2. Plasma concentrations of adrenaline and noradrenaline were significantly higher during the mental stress activity than at baseline measurement ($p < 0.01$).

Baseline CBF and MBF and values obtained during the mental stress activity are given in Table 3. CBF of the cerebellum and putamen was significantly increased during mental stress ($p < 0.01$–0.05); however, no significant change was observed in CBF of the whole cerebrum. MBF was significantly increased during the mental stress activity ($p < 0.05$). Percent changes in CBF of the whole cerebrum and MBF during the mental stress activity are shown in Figure 1. Percent change in CBF of the whole

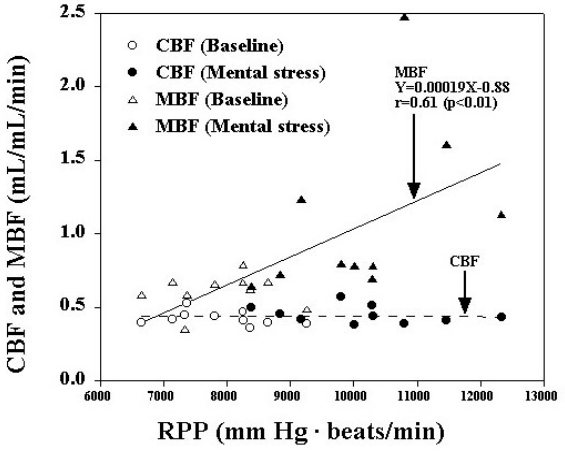

Fig. 3 Correlations between RPP values and values of CBF of the whole cerebrum and MBF recorded at baseline and during mental stress activity.

cerebrum was 6% ± 11% and that in MBF was 78% ± 73% (mean ± SD). Percent changes in regional CBF during mental stress are shown in Figure 2. Percent change in CBF of the cerebellum was 22% ± 18% (mean ± SD).

According to the anatomic standardization analysis using SPM99, significant relative hyperperfusion during the mental stress activity was observed in the bilateral cerebellum, bilateral thalamus, right insular cortex, right superior temporal gyrus, bilateral inferior frontal gyrus, bilateral precentral gyrus, bilateral anterior part of the cingulate gyrus, and left angular gyrus ($p < 0.001$).

Correlations between RPP and values of CBF of the whole cerebrum and MBF at baseline measurement and during mental stress activity are shown in Figure 3. A significant positive correlation was observed between RPP and MBF ($p < 0.01$), but not between RPP and CBF.

DISCUSSION

Blood pressure, heart rate, RPP, and plasma concentrations of adrenaline and noradrenaline were significantly greater during mental stress activity than at baseline measurement (Tables 1, 2), indicating that the mental stress induced in the present study caused a substantial sympathetic response.[1–4] Because of this sympathetic response, MBF was significantly increased during mental stress (Table 3, Fig. 1), supporting the hypothesis that mental stress can be used for estimation of coronary flow reserve in patients with coronary artery disease.[7] RPP represents the work load of the heart, and therefore a significant positive correlation was observed between RPP and MBF (Fig. 3). In addition, changes in RPP and plasma concentration of noradrenaline in relation to mental stress also correlated significantly (data not shown).

No significant difference was observed in P_aCO_2 between the mental stress and baseline conditions (Table 1), indicating a lack of effect of P_aCO_2 on the change in CBF in relation to mental stress in the present study. Significant relative hyperperfusion was observed in relation to mental stress bilaterally in the cerebellum, and absolute CBF in the cerebellum was also significantly increased (Table 3, Fig. 2). Several authors have reported that linguistic processing,[27,28] attentional processing,[29] and working memory tasks[30,31] cause cerebellar activation. A significant increase in CBF in the cerebellum in relation to mental stress might be caused by such neural activations. Significant relative hyperperfusion during mental stress was also observed in several regions in the cerebrum, indicating neural activations due to linguistic processing, attentional processing, and working memory tasks that were caused by the mental stress protocol carried out in the present study. Neural activation in the precentral gyrus can be caused by linguistic processing[27]; neural activation in the anterior cingulate can be caused by attentional processing[32]; and neural activation in the insular cortex, superior temporal gyrus, inferior frontal gyrus, and angular gyrus can be caused by working memory tasks.[30] It has been reported that mental activity and attentional processing can cause neural activation in the thalamus.[33,34] Although we observed significant relative hyperperfusion in relation to mental stress in several regions in the cerebrum, no significant increase in absolute CBF in relation to mental stress was observed in the whole cerebrum (Table 3, Fig. 1), similar to results reported previously.[11]

Mental stress causes a sympathetic response (Tables 1, 2),[1–4] and the sympathetic innervation of intracranial arteries contributes to the regulation of cerebral perfusion.[12,13] Sympathetic stimulation caused cerebral vasoconstriction and reduced CBF in cats[14] and in dogs,[15] whereas parasympathetic stimulation increased CBF in cats.[17] However, we observed no significant decrease in CBF during mental stress in any brain region or in the whole cerebrum (Table 3). Because mental stress might be associated with a diffuse and widespread activation of the brain, a decrease in CBF due to sympathetic stimulation might be canceled out.

RPP, which represents the work load of the heart, was significantly greater in relation to mental stress than at baseline measurement, indicating that cardiac output may increase during mental stress. Therefore, MBF was significantly correlated with the RPP (Fig. 3). However, no correlation was observed between the RPP and CBF of the whole cerebrum (Fig. 3). This indicates that CBF is independent of the cardiac output due to autoregulation of the CBF.[35] It has been reported, however, that hyperdynamic therapy with dobutamine on patients with cerebral vasospasm following subarachnoid hemorrhage causes an increase in CBF while maintaining the blood pressure in a normal range.[36]

In conclusion, changes in CBF and MBF in relation to mental stress were measured in human subjects by the

dual-PET system. The MBF, blood pressure, heart rate, and plasma concentrations of adrenaline and noradrenaline increased significantly during mental stress. Although these sympathetic responses were observed during this type of stress, no significant change in CBF of the whole cerebrum was observed, even though sympathetic stimulation causes cerebral vasoconstriction and reduces CBF in animals.

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