Figure3
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Figure5

CBF (0-40 ml/g/min) MTT (0-6sec) CBV (0-2 ml/ml)

Heart and Brain Circulation and CO2 in Healthy Men

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Abstract

Aim: To compare blood flow response to arterial carbon dioxide tension change in the heart and brain of normal elderly men.

Methods: Thirteen healthy elderly male volunteers were studied. Hypercapnea was induced by carbon dioxide inhalation and hypocapnea was induced by hyperventilation. Myocardial blood flow (mL•minute^{-1}•[100 gram of perfusable tissue]$^{-1}$) and cerebral blood flow (mL•minute^{-1}•[100 gram of perfusable tissue]$^{-1}$) were measured simultaneously at rest, under carbon-dioxide gas inhalation and hyperventilation using the combination of two positron emission tomography scanners.

Results: Arterial carbon dioxide tension increased significantly during carbon dioxide inhalation (43.1 ± 2.7 mmHg, $p < 0.05$) and decreased significantly during hyperventilation (29.2 ± 3.4 mmHg, $p< 0.01$) from baseline (40.2 ± 2.4 mmHg). Myocardial blood flow increased significantly during hypercapnea (88.7 ± 22.4, $p < 0.01$) from baseline (78.2 ± 12.6), as did the cerebral blood flow (baseline: 39.8 ± 5.3 vs. hypercapnea: 48.4 ± 10.4, $p < 0.05$). During hypocapnea cerebral blood flow decreased significantly (27.0 ± 6.3, $p < 0.01$) from baseline as did the myocardial blood flow (55.1 ± 14.6, $p < 0.01$). However normalized myocardial blood flow by cardiac workload (100mL•mmHg^{-1}•[heart-beat]$^{-1}$•[gram of perfusable tissue]$^{-1}$) was not changed from baseline (93.4 ± 16.6) during hypercapnea (90.5 ± 14.3) but decreased significantly from baseline during hypocapnea (64.5 ± 18.3, $p < 0.01$).

Conclusion: In normal elderly men, hypocapnea produces similar vasoconstriction in both heart and brain. Mild hpercapnea increased cerebral blood flow but did not have an additional effect to dilate coronary arteries beyond the expected range in response to an increase in cardiac workload.

Introduction

Correlation between arterial carbon dioxide tension and cerebral blood flow is well established [Kety & Schmidt 1948, Shimosegawa et al. 1995, Kuwabara et al. 1997]. However, responsiveness of myocardial blood flow to hypercapnea and hypocapnea has not been fully elucidated. These relationships were investigated in animal experiments [Feinberg et al. 1960, Love et al. 1965, Case & Greenberg 1976, Bos et al. 1979, Powers et al. 1986] and human clinical studies [Rowe et al. 1962, Neill & Hattenhauer 1975, Wilson et al. 1981, Kazmaier et al. 1998] with conflicting results. The inconsistencies observed should be attributable to differences in experimental conditions, such as the techniques used for measurement, or whether the studies were performed in animals or humans, or presence versus absence of ischemic heart disease.

In this study, we evaluated the responses of myocardial blood flow and cerebral blood flow to hypercapnea and hypocapnea in healthy elderly men. We employed a dual positron emission tomography (PET) scanner consisting of two scanners to measure myocardial blood flow and cerebral blood flow simultaneously in the same subject [Iida et al. 1998]. PET allows assessment of functional parameters under physiological conditions. Using this dual PET scan technique allowed simultaneous assessment of myocardial and cerebral circulations, noninvasively and reliably and enabled comparison of the two.

Materials and Methods

Study Subjects

Thirteen healthy men (age range 51-71 years; mean 59.4, standard deviation [5.5]) who had been the subjects of previously published studies with different objectives [Iida et al. 1998, Ito et al. 1999, Ito et al. 2000, Ito et al. 2002] took part in the study. These men had normal laboratory parameters, no signs or symptoms of ischemia in the heart or brain, and no abnormalities were found by brain magnetic resonance imaging, electrocardiography, cardiac echocardiography, and physical examination. All subjects provided written informed consent that data obtained from the PET studies could be used for research purposes. The study protocol was approved by the Ethics Committee of the Research Institute of Brain and Blood Vessels, Akita, Japan.

PET Procedures

The Headtome V dual PET system (Shimadzu Corp., Kyoto, Japan), a combination of the two Headtome V PET scanners, was used for all studies [Iida et al. 1998]. The system allowed simultaneous imaging of the brain and heart and provided 47 sections for the brain and 31 sections for the heart with center-to-center distances of 3.125 mm. The intrinsic spatial resolution was 4.0 mm in-plane and 4.3 mm full-width at half-maximum axially. All PET data were acquired in 2D mode and reconstructed with a Butterworth filter, resulting in a final in-plane resolution of approximately 8 mm full-width at half-maximum.

After an overnight fast, subjects were placed in the supine position on the scanner bed. The blood-pool images were obtained 1 minute after continuous inhalation of ^{15}O-CO gas (approximately 5 GBq total applied to the mouth). One minute after the end of ^{15}O-CO gas inhalation, ^{15}O-CO blood-pool images of the heart were obtained with an R-wave triggered electrocardiogram gated tomographic scan. A simultaneous gated static scan on both the heart and brain was done 4 minutes after the inhalation of ^{15}O-CO gas. Three venous blood samples were taken during the ^{15}O-CO scan, and the radioactivity concentration in the whole blood was measured using a NaI-well counter that was cross-calibrated with the PET scanner. ^{15}O-CO blood-pool images were used to draw regions of interests on left ventricular cavity and left ventricular wall accurately to obtain time activity curves. The recovery of

coefficient of left ventricular cavity was given by the myocardial static blood volume image and was also used to determine myocardial blood flow [Iida et al. 1998]. After 12-15 minutes, to allow for decay of ^{15}O-radioactivity to background levels, transmission scanning was undertaken over 10 minutes. Then, H_2^{15}O PET studies were performed at rest, and under hypercapnea and hypocapnea. The order of the studies was rest, hypercapnea, and hypocapnea studies in 7 subjects, and rest, hypocapnea, and hypercapnea studies in 6 subjects. The intervals between H_2^{15}O PET studies were at least 15 minutes to allow the decay of radioactivity. Following the continuous intravenous infusion of H_2^{15}O (1.1-1.4 GBq) over 2 minutes, 180-sec static imaging of the brain and 360-sec dynamic imaging of the heart were commenced. The dynamic data of the heart consisted of twelve 5- seconds frames, eight 15-seconds frames, and six 30- seconds frames. Hypercapnea was achieved by inhalation of 7% CO_2 gas, beginning 1 minute before ^{15}O-water injection and continuing until the end of the imaging of the heart. Hypocapnea was induced by hyperventilation. Three arterial blood samples were taken during each PET scan to measure arterial carbon dioxide tension and pH.

Data Analysis

Cerebral blood flow images were generated from the PET data as described previously [Iida et al. 1998], and a region of interest for the inside of the brain contour was drawn on a slice of the cerebral blood flow image that was at the level of the basal ganglia. The region of interest was determined on an image obtained at rest and applied to images obtained under stress conditions. The mean cerebral blood flow in the region of interest was calculated from ^{15}O-H_2O autoradiography method [Raichle ME et al. 1983] and used for the following analyses. The percent change in cerebral blood flow at hypercapnea was defined as $100 \times$ (cerebral blood flow at hypercapnea - cerebral blood flow at rest) / cerebral blood flow at rest, and cerebral blood flow responsiveness to hypercapnea was calculated as percent change in cerebral blood flow at hypercapnea divided by arterial carbon dioxide tension at hypercapnea minus arterial carbon dioxide tension at rest. The percent change in cerebral blood flow at hypocapnea and cerebral blood flow responsiveness to hypocapnea were determined using similar calculations, but using hypocapnea values instead.

The region of interests for the left ventricular cavity and the whole anterolateral wall

of the left ventricle at mid ventricular level were drawn on a slice of the short-axis myocardial images. The region of interests for the image at rest were copied on the myocardial images under the stress conditions. The myocardial blood flow value was estimated using the regions of interests according to a previously validated method [Iida et al. 1998]. In summary, myocardial blood flow was calculated using a non-linear least squares fitting technique of the left ventricular tissue and arterial ^{15}O-H_2O time activity curves [Iida H et al. 1988]. The input function was non-invasively determined from the time activity curve of left ventricular cavity [Iida H et al. 1992]. Time activity curve of the left ventricular cavity and that of the myocardial wall were fitted to the previously demonstrated tracer kinetic model equations to determine myocardial blood flow [Iida et al. 1998]. The percent change in myocardial blood flow at hypercapnea was defined as $100 \times$ (myocardial blood flow during hypercapnea - myocardial blood flow at rest) / myocardial blood flow at rest, and myocardial blood flow responsiveness to hypercapnea was calculated as percent change in myocardial blood flow during hypercapnea divided by arterial carbon dioxide tension under hypercapnea minus arterial carbon dioxide tension at rest. The percent change in myocardial blood flow during hypocapnea and myocardial blood flow responsiveness to hypocapnea were determined using similar calculations but using hypocapnea values instead. In addition, normalized myocardial blood flow was calculated for the rate pressure product by the equation:

Normalized myocardial blood flow = $10000 \times$ myocardial blood flow / rate pressure product, and percent change in normalized myocardial blood flow and normalized myocardial blood flow responsiveness were calculated.

Statistical Analysis

Values were expressed as the mean ± standard deviation. Comparisons were made by one-way analysis of variance followed by Fisher's least significant difference tests for parametric distributions and Kruskal-Wallis test followed by Scheffe's test for nonparametric distributions. A P value < 0.05 was considered statistically significant.

Results

Hemodynamics

Blood pressures, heart rate, rate pressure product, arterial carbon dioxide tension and pH are summarized in Table 1. Blood pressures were measured in the thigh because arteries and veins in both arms were cannulated. Since the blood pressure measured in the thighs were on average 25 mmHg higher than those measured in the arms in our institution, blood pressures in the thigh were considered to be within normal range. Electrocardiogram findings under hypercapnea or hypocapnea did not change compared with those at rest. Arterial carbon dioxide tension significantly decreased during hypocapnea and significantly increased during hypercapnea. Blood pressures significantly increased during hypercapnea but remained unchanged during hypocapnea. Rate pressure product did not change significantly during hypocapnea but significantly increased during hypercapnea.

Cerebral blood flow

Cerebral blood flow significantly decreased during hypocapnea and significantly increased during hypercapnea (Table2). The change in cerebral blood flow caused by hypocapnea was -32.2 percent ± 11.3 percent, and the cerebral blood flow responsiveness to hypocapnea was 3.0 ± 1.1 percent /mmHg. The change in cerebral blood flow caused by hypercapnea was 21.0 percent ± 15.5 percent, and the cerebral blood flow responsiveness to hypercapnea was 8.2 ± 5.3 percent /mmHg.

Myocardial blood flow

Hypocapnea caused a significant reduction in myocardial blood flow from baseline (Table 2). The percent change in myocardial blood flow caused by hypocapnea was -29.3 percent ± 15.1 percent, and the myocardial blood flow responsiveness to hypocapnea was 3.5 ± 3.0 percent /mmHg. Normalization for rate pressure product did not alter the percent change (- 30.4 percent ± 16.5 percent) and responsiveness (-2.2 ± 11.2 percent /mmHg) substantially. Under hypocapnea, the percent changes in cerebral blood flow, myocardial blood flow, and normalized myocardial blood flow were not significantly different compared with baseline. There were no significant differences in the responsiveness to hypocapnea between cerebral blood flow, myocardial blood flow, and normalized myocardial blood flow.

Hypercapnea significantly increased myocardial blood flow. The percent change in myocardial blood flow caused by hypercapnea was 12.5 percent ± 15.6 percent, and the myocardial blood flow responsiveness to hypercapnea was 5.2 ± 9.9 percent /mmHg. However, the increase in myocardial blood flow disappeared after normalization for rate pressure product. The change in normalized myocardial blood flow under hypercapnea was -2.2 percent ± 11.2 percent, and the normalized myocardial blood flow responsiveness to hypercapnea was -1.7 ± 8.8 percent /mmHg. As for hypercapnea, the percent change in normalized myocardial blood flow was significantly smaller than the change in cerebral blood flow ($p < 0.05$), and the normalized myocardial blood flow responsiveness was significantly smaller than cerebral blood flow responsiveness ($p < 0.05$).

Discussion

We simultaneously measured myocardial blood flow and cerebral blood flow at rest, during hypocapnea, and during hypercapnea in healthy elderly men. During hypocapnea, cerebral blood flow was reduced significantly as expected, and myocardial blood flow also diminished significantly to a similar magnitude. Rate pressure product did not change significantly from baseline, and myocardial blood flow normalized for rate pressure product also decreased. These results indicate that hypocapnea depresses myocardial blood flow, independently of cardiac workload, in healthy elderly men. The responsiveness to hypocapnea was similar between cerebral blood flow and myocardial blood flow, suggesting that hypocapnea can induce vasoconstriction in both heart and brain in healthy elderly men.

Several studies of coronary vascular response to hypocapnea using experimental animals have been reported however, the results were inconsistent [Feinberg 1960, Love 1965, Case 1976]. In a study of humans **with** negligible coronary artery disease, hypocapnea with 30.6 percent reduction in arterial carbon dioxide tension resulted in a significant 30.3 percent reduction in myocardial blood flow with a wide range of variability [Rowe 1962]. The present results are consistent with these previous studies. However, in studies of patients with coronary artery disease, hypocapnea resulted in a mild but significant 12 percent reduction in myocardial blood flow [Neill & Hattenhauer 1975] or did not change significantly [Wilson et al. 1981, Kazmaier et al. 1998]. Therefore, myocardial blood flow response to hypocapnea is likely to be different between normal subjects and patients with coronary artery disease. Since myocardial blood flow response to hypocapnea did not differentiate regions with myocardial ischemia from regions of non-ischemic myocardium in these studies of coronary artery disease, further study is required to clarify whether myocardial blood flow response to hypocapnea would differ between ischemic myocardium and non-ischemic myocardium.

Myocardial blood flow response to hypercapnea remains controversial. A number of experimental animal studies showed that hypercapnea did not increase myocardial blood flow [Feinberg et al. 1960, Love et al. 1965, van den Bos et al. 1979], whereas other studies showed that hypercapnea could increase myocardial blood flow [Case & Greenberg 1975, Powers et al. 1986]. In a study of anesthetized patients with coronary artery disease before

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surgery, elevation of arterial carbon dioxide tension (+10 mmHg) resulted in a 15 percent increase in myocardial blood flow [Kazmaier et al. 1998]. However, the study did not estimate normalized myocardial blood flow to exclude the influence of cardiac workload on myocardial blood flow measurement [Kazmaier et al. 1998]. In this study, hypercapnea significantly increased myocardial blood flow and cerebral blood flow but not normalized myocardial blood flow with rate pressure product in healthy elderly men. Myocardial blood flow responsiveness to hypercapnea was significantly lower than that in cerebral blood flow when myocardial blood flow was normalized with respect to rate pressure product. Increase in cardiac workload under hypercapnea could explain an increase in myocardial blood flow. However, hypercapnea did not have an additional direct effect to increase myocardial blood flow independent of an elevation in cardiac workload under mild hypercapnea. Since myocardial blood flow responsiveness to hypercapnea was significantly lower than that in cerebral blood flow when myocardial blood flow was normalized with respect to cardiac workload, vascular responsiveness to hypercapnea is expected to be different between heart and brain. In this study, the magnitude of increase in arterial carbon dioxide tension during hypercapnea was small (3 mmHg), contrasting with the magnitude of decrease in arterial carbon dioxide tension during hypocapnea (11 mmHg). Such difference in the magnitude of changes in arterial carbon dioxide tension may explain why hypocapnea was effective to decrease the normalized myocardial blood flow but hypercapnea had no effect to increase the normalized myocardial blood flow. However, even under such very small increase in carbon dioxide tension, significantly elevated myocardial blood flow without normalization in response to an increase in cardiac workload was seen. Therefore, the importance of the carbon dioxide tension changes in determining the response of heart and brain perfusion could be discussed more than is presently done. To resolve such issues, much stronger hypercapneic stress test at different hypercapnic levels to increase arterial carbon dioxide tension is required to clarify whether hypercapnea directly increases myocardial blood flow independent of an increase in cardiac workload. Use of beta-blockers to exclude an influence of increase in cardiac workload for the myocardial blood flow measurement during hypercapnea [van den Bos et al. 1979, Powers et al. 1986] would also be helpful to understand myocardial blood

flow responsiveness to hypercapnea. For future studies, it is of interest to test the effect of normalization with both cardiac workload and arterial carbon dioxide tension changes on the studies of myocardial blood flow.

Conclusion

In normal elderly men, hypocapnea produces similar vasoconstriction in both heart and brain. Mild hpercapnea increased cerebral blood flow but did not have an additional effect to dilate coronary arteries beyond the expected range in response to an increase in cardiac workload.

Conflict of interest

No conflict of interest exists in connection with this article.

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Table 1. Hemodynamics, arterial carbon dioxide tension and pH during $H_2^{15}O$ PET studies

	Rest	Hypercapnea	Hypocapnea
Systolic blood pressure (mmHg)	146.5 ±20.9	159.8 ±25.4	144.8 ±26.7
Diastolic blood pressure (mmHg)	82.8 ±12.0	85.3 ±10.7	78.5 ±13.2
Heart rate (beat / minute)	58.4 ±7.8	61.6 ±8.7	60.7 ±7.8
Rate pressure product	8472 ±1146	9758 ±1609	8717 ±1677
Arterial carbon dioxide tension	40.2 ±2.4	43.1 ±2.7* $	29.2 ±3.4† $
pH	7.417 ±0.013	7.385 ±0.019 $	7.505 ±0.039 $

Data are presented as mean ± standard deviation.

Significance of changes compared with the three groups: *P<0.05, †P<0.01 by Fisher PLSD,

Significance of changes compared with the resting condition:　　P<0.05, $ P < 0.01 by Wilcoxon signed rank test