Originals

LCBF values decline while Lx values increase during normal human aging measured by stable xenon-enhanced computed tomography

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Summary. Results of measurements of LCBF and Lx values utilizing optimal CT-CBF methods under resting conditions are reported among thirty-two neurologically normal volunteers aged between 20 and 88 years. Measurements were made during inhalation of 26-30% stable xenon gas for 8 min and serial scanning utilizing a state-of-the-art CT scanner with both eyes closed and ears unplugged. LCBF values for cortical gray matter were lowest in occipital cortex and highest in frontal cortex. Gray matter flow values were also high in subcortical structures with highest values measured in the thalamus. For white matter, highest flow values were measured in the internal capsule. Changes in LCBF and Lx values were analyzed with respect to advancing age. Significant age-related declines in LCBF values were observed in occipital cortex and frontal white matter. Significant age-related increases in Lx values were measured in frontal and temporal cortex, caudate nucleus and thalamus. Possible explanations are offered for these age-related increases in Lx values for gray matter, such as accumulation of lipofuscin in neurons and relative compacting of gray matter with advancing age. The latter increases the numbers of nerve cells sampled per volume of gray matter measured.

Key words: Cerebral blood flow - Partition coefficient - Computed tomography - Stable xenon - Aging

Increased survival of the elderly among populations of developed countries has stimulated interest in the biology of normal aging and age-related disorders, particularly dementia. Declines in cerebral blood flow (CBF) associated with normal aging have been of long-standing interest and were controversial at one time. Kety first reported age-related declines in CBF and cerebral metabolic rate for oxygen (CMRO2) for the entire brain [1]. This study was based on a review of reported cases of CBF and CMRO2 measured among different age groups utilizing the nitrous oxide inhalation method which provides average values for CBF and CMRO2 without regional information. The method used is also invasive.

Over the past 40 years, a number of different methods have been developed for measuring CBF in humans. The intracarotid injection of radioactive krypton (88Kr) and xenon (133Xe) made possible concurrent measurements of regional CBF throughout one hemisphere [2, 3]. Later, intravenous injection of 133Xe was used [4]. However, for purposes of studying aging in normal volunteers, invasive methods are undesirable. All the methods so far mentioned require carotid and/or jugular puncture or catheterization of an antecubital vein.

The 133Xe inhalation method for measuring regional CBF has the advantage of being entirely noninvasive [5-7], but also has several disadvantages. Certain assumptions must be made, including the assignment of fixed values for xenon brain-blood partition coefficients (Lx values) for both gray and white matter. These assigned values were fixed after deriving them from measurements made in vitro from dissected samples of dead brain [8]. Since CBF values are derived from the product of Lx values and flow rate constants (k), optimal methods for determining local CBF (LCBF) values require measurement of Lx values in vivo since they may become altered with advancing age and disease [9]. Another disadvantage of the two-dimensional 133Xe method is that information is not provided concerning LCBF values for deep brain structures including the basal ganglia. The development of tomographic methods during the past ten years, such
as single-photon emission computed tomography (SPECT), positron emission tomography (PET) and stable xenon computed tomography (CT-CBF), has made possible measurements of LCBF values for the deep brain structures [10]. A considerable advantage of the CT-CBF method is that $L_A$ values may be measured in vivo, rendering LCBF values more accurate [11, 12].

The CT-CBF method is practical and accurate [13-15], however, normative values for reference when utilizing modern CT scanners for CBF measurements among sizable groups of different ages are not available for comparison with similar measurements made in diseased states, particularly among the elderly. Relatively few studies have described normal values utilizing CT-CBF methods [16-18]. Tachibana et al. [16] reported LCBF and $L_A$ values among 20 normal volunteers having an age range between 20 and 100 years. Segawa [17] reported 7 cases whose ages ranged between 22 and 56 years. Gotoh et al. [18] reported LCBF values among 10 normal subjects with a mean age of 38 ± 7 years. In earlier reports, only older CT scanners were available with one-minute scanning times. Likewise, slow and less efficient xenon delivery systems were used. For these reasons, LCBF and $L_A$ values were less accurate than is possible utilizing state-of-the-art CT scanners, with scanning times of a few seconds, which minimizes motion artifact. Efficient xenon delivery systems have also become available which enable rapid and more reliable saturation of arterial blood and brain tissues [19].

Morphometric studies of human brains from the elderly report structural changes of gray matter with advancing age which may alter the solubilities of xenon gas in gray matter and thereby alter $L_A$ values for gray matter [20, 21]. In earlier reports, utilizing less optimal methods, $L_A$ values appeared to remain unchanged with advancing age [6]. To respond to such methodological questions and to elucidate possible changes in $L_A$ values attributable to aging, LCBF and $L_A$ values have been measured by the xenon contrast CT-CBF method utilizing a state-of-the-art CT scanner, plus an efficient Xenon gas delivery system. These optimal methods have been applied to measurements of LCBF and $L_A$ values among 32 neurologically normal volunteers with greater accuracy than formerly possible.

Description of volunteers and methods

The population studied consisted of 32 neurologically normal volunteers (17 men, 15 women) aged between 20 and 88 years. Their ages categorized by decades were as follows: 20–29 years of age ($n=3$); 30–39 ($n=1$); 40–49 ($n=2$); 50–59 ($n=12$); 60–69 ($n=10$); 70–79 ($n=2$); 80–89 ($n=2$). This cohort of volunteers were recruited by means of magazine articles published in the local press describing ongoing longitudinal and cross-sectional studies of normal aging and by seeking volunteers among the friends and relatives of investigators and patients [22].

Volunteers were admitted to the study if, after examination, they were found to be neurologically normal and without history, signs or symptoms of pulmonary disease. They were all active, self-supporting people who were in good health. Nineteen had risk factors for stroke (hypertension $n=10$; diabetes mellitus $n=2$; hyperlipidemia $n=11$; heart disease $n=3$), the remainder had none. All underwent general physical and neurological examinations including psychometric testing utilizing the Cognitive Capacity Screening Examination [23]. These volunteers showed no abnormalities on CT scanning other than age-associated brain atrophy. They were told not to take any medication at the time of the CBF measurements.

Prior to measurements of LCBF and $L_A$, all volunteers signed informed consent. At this time, the procedure was described and it was explained that inhalation of stable xenon gas often causes transient paraesthesias of the hands and feet and a brief sensation of "drowsiness" or "light-headedness". The importance of maintaining the head motionless during each CBF measurement was also explained. All volunteers fasted for 4 h prior to the CBF measurement. Consent forms and protocols describing the CT-CBF measurements have been approved annually by the Institutional Review Board of the Veterans Administration Medical Center, Houston, Texas, USA.

Detailed descriptions of the methods utilized for measuring LCBF and $L_A$ values have been described in earlier publications [11, 12, 19]. CT-CBF measurements were performed utilizing a state-of-the-art CT scanner (SOMATOM DR Version H, Siemens Medical Systems, Inc., Iselin, New Jersey, USA), with high reproducibility and uniformity of scanned fields. These are important performance characteristics for quantitative CT applications as reviewed for the present application [19, 24, 25]. The scanning method uses factors of 96 kVp, 540 mAs, 8 mm slice thickness and 5-second scanning times for each scan in the serial CT measurements, plus reconstruction parameters of 2.2 zoom factor and standard head kernel utilizing the MS05 version C1 SOMATOM DR scan program software. Inhalation of 100% oxygen was begun for 3 min before chang-