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Prolonged Hypocapnia Does Not Alter the Rate of CSF Production in Dogs during Halothane Anesthesia or Sedation with Nitrous Oxide

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This study examined the effect of prolonged hypocapnia on the rate of cerebrospinal fluid (CSF) production ($\dot{V}_f$) and on other CSF dynamics in dogs. Determination of CSF values began 2 h after the onset of hypocapnia and continued for an additional 3 h. Two separate methods were used to determine $\dot{V}_f$: modified open ventriculocisternal perfusion and closed ventriculocisternal perfusion. Dogs were examined both during hypocapnia plus anesthesia with halothane (0.8%) and nitrous oxide (66%), and during hypocapnia plus sedation with nitrous oxide (66%) and halothane (0.15%) combined with bupivacaine (0.75%) infiltration of wound edges. There were no differences in $\dot{V}_f$ measured by the two methods. At the first measurable time period, mean $\dot{V}_f$ values during hypocapnia and halothane anesthesia, 32 ± 9 and 35 ± 10 μl/min (mean ± SD), were lower than mean $\dot{V}_f$ values during hypocapnia and nitrous oxide sedation, 48 ± 11 and 49 ± 8 μl/min. $\dot{V}_f$ did not change significantly during 3 h of hypocapnia. For both halothane anesthesia and nitrous oxide sedation, mean $\dot{V}_f$ values during hypocapnia were not significantly different from $\dot{V}_f$ values previously reported during normocapnia, 31 ± 12 and 33 ± 12 μl/min and 44 ± 13 and 47 ± 14 μl/min, respectively. The results indicate that prolonged hypocapnia does not decrease $\dot{V}_f$, and, therefore, reduction of $\dot{V}_f$ is probably not one of the causes for reduction of elevated CSF pressure by prolonged hypocapnia. Regarding the other data on CSF dynamics, CSF pressure at hypocapnia was similar to that at normocapnia, suggesting that hypocapnia did not affect resistance to reabsorption of CSF. CSF pressure during hypocapnia and nitrous oxide sedation was similar to that during hypocapnia and halothane anesthesia, even though $\dot{V}_f$ was lower during halothane. This suggests that resistance to reabsorption was greater during halothane anesthesia than during sedation with nitrous oxide. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane. Brain: intracranial pressure. Carbon dioxide: hypocapnia. Cerebrospinal fluid: pressure; production; volume.)

HYPOCAPNIA IS OFTEN USED for prolonged periods to reduce elevated cerebrospinal fluid (CSF) pressure. One means by which hypocapnia may reduce CSF pressure is by lowering cerebral blood volume (CBV). Hypocapnia initially causes constriction of cerebral blood vessels, but, over a period of several hours, cerebral vessels re-expand.[1] Another means by which hypocapnia may reduce CSF pressure is by altering CSF dynamics—the rate of CSF production ($\dot{V}_f$), the rate of reabsorption of CSF ($\dot{V}_a$), resistance to reabsorption of CSF (R_a), and CSF volume. In contrast to the cerebral vascular effects of hypocapnia, little is known of the effects of prolonged hypocapnia on CSF dynamics.

Three studies examining the effect of prolonged hypocapnia on $\dot{V}_f$ present conflicting results.[2–4] Oppelt *et al.* reported that 4–5 h of hypocapnia decreased $\dot{V}_f$ in pentobarbital-anesthetized dogs.[2] In contrast, Martins *et al.* reported that 2.5–3 h of hypocapnia did not change V_f in monkeys anesthetized with phencyclidine and pentobarbital.[3] In agreement with the latter study, Hochwald *et al.* reported that 4–4.5 h of hypocapnia did not change $\dot{V}_f$ from normal values in pentobarbital-anesthetized cats.[4] No studies have examined the effects of prolonged hypocapnia on $\dot{V}_a$, R_a, or CSF volume.

The conflicting results regarding the effect of hypocapnia on $\dot{V}_f$ could relate to the methodology used; namely, classical open ventriculocisternal perfusion. With this technique, CSF pressure is arbitrarily fixed at a value that is determined by the location of the tip of the CSF outflow cannula. By convention, the tip of the outflow cannula is set at the level of the external auditory meatus, and a fixed, standardized CSF pressure is achieved for the entire experimental group. However, this technique sets CSF pressure at a value that may not be the one normally occurring in the intact animal. Previous studies by others on variables which affect open ventriculocisternal perfusion suggest that CSF pressure set above that which is usual may cause an underestimation of $\dot{V}_f$, while low CSF pressure may cause an overestimation of $\dot{V}_f$.[5,6] Thus, a source for error in the determination of $\dot{V}_f$ may have been introduced in the previous studies of prolonged hypocapnia.

The present studies were designed to examine the effects of prolonged hypocapnia on CSF dynamics. We compared two techniques of ventriculocisternal perfusion that were designed to eliminate the potential source for error noted above. The techniques used for the present studies, closed ventriculocisternal perfusion and modified open ventriculocisternal perfusion, differed from the classical technique because CSF pressure was not fixed at a pre-determined value, but, rather,

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was individualized to each animal. Closed ventriculocisternal perfusion permitted $\dot{V}_f$ to be determined and inferences to be made about R_a and CSF volume.[7] Modified open ventriculocisternal perfusion permitted $\dot{V}_f$ and $\dot{V}_a$ to be determined.[8] CSF dynamics were examined both during sedation plus analgesia and during anesthesia. These two experimental conditions were chosen as models of clinical situations where prolonged hypocapnia frequently is used; namely, in critical care settings and during operative procedures.

Methods

Animal Preparation

This study was approved by the Animal Care Committee of the University of Washington. Twenty-four unmedicated mongrel dogs (weights 14–20 kg) were studied. Anesthesia was induced with halothane (>1.2%, end expired value determined intermittently by gas chromatography) and nitrous oxide (N_2O, 66%, inspired) in oxygen (O_2). The trachea was intubated and ventilation was controlled. Muscle paralysis was maintained in all dogs with a continuous infusion of succinylcholine. The right femoral artery was cannulated to permit arterial blood sampling for blood gas analysis and to permit continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. A urinary catheter was placed, the right femoral vein was cannulated for fluid and drug administration, expired CO_2 was continuously monitored, and temperature was monitored by a nasopharyngeal thermistor probe.

A burr hole was placed over the left hemisphere, and a catheter was directed into the underlying lateral ventricle. The posterior neck muscles were surgically separated to expose the atlanto-occipital membrane, and a catheter was directed into the cisterna magna. A 0.3 ml sample of CSF was obtained from the cisternal cannula for measurement of osmolality using a Wescor Model 5100 B Vapor Pressor Osmometer (Wescor, Inc., Logan, UT). Mock CSF of matching osmolality was prepared by mixing standard solutions[9] (osmolality 290, 300, or 310 mOsm/kg) labeled with Blue Dextran (1 mg/ml) (Sigma Chemical Co., St. Louis, MO). Wound edges were infiltrated with bupivacaine (0.75%), and the concentration of halothane was decreased (N_2O unchanged) to 0.8% in 12 dogs ("halothane anesthesia" group) and to 0.15% in the other 12 dogs ("N_2O sedation" group). Details of this animal preparation were previously reported.[7,10]

Closed Ventriculocisternal Perfusion

Six of the 12 dogs receiving halothane anesthesia and six of the 12 dogs receiving N_2O sedation were prepared for closed ventriculocisternal perfusion. Minute ventilation was set to maintain Pa_{CO_2} at about 20 mmHg. Mock CSF was infused into the ventricle and the mixture of mock and native CSF withdrawn from the cisterna magna using a Harvard dual syringe pump (Harvard Infusion/Withdrawal Pump, Model 941, Harvard Apparatus, An Ealing Company, South Natick, MA). The infusion and withdrawal rates were 30 μl/min. The flow-through cuvette of a Turner spectrophotometer (Turner Spectrophotometer, Model 330, Turner Associates, Palo Alto, CA) was positioned in the withdrawal line. This arrangement did not alter CSF pressure from the value normally occurring in the intact animal because the perfusion system was closed and the rate of infusion equalled the rate of withdrawal. Ventricular and cisternal CSF pressures were monitored continuously to insure that pressures did not change significantly from pre-perfusion values. This initial period of ventriculocisternal perfusion allowed for equilibration of labeled mock CSF with native CSF in the intracerebral and cisternal CSF spaces of the dog. The concentration of Blue Dextran in the cisternal outflow solution was determined continuously as the solution passed through the spectrophotometer cuvette. Concentrations of Blue Dextran were determined using light absorbence at 620 nm. Light absorbance values from the spectrophotometer were recorded continuously on a Gould polygraph so that, at any moment, it could be determined whether the displayed light absorbence value was truly representative or a momentary fluctuation. Details of this technique were previously reported.[7]

The time to equilibration of the Blue Dextran tracer (T_{eq}) was defined as the time when measured tracer concentration in the cisternal outflow varied by ≤2% over 30 min. $\dot{V}_f$ was determined at the time of tracer equilibration and at 45, 90, 135, and 180 min following tracer equilibration. $\dot{V}_f$ was calculated as previously described[11], according to the formula of Heisey *et al.*[8] (Appendix). CSF pressure and systemic variables also were recorded at the time of tracer equilibration and at 45, 90, 135, and 180 min following tracer equilibration. The initial volume of distribution of the tracer (VD_x) was calculated according to the formula of Pappenheimer *et al.*[12] (Appendix).

Modified Open Ventriculocisternal Perfusion

The other six of 12 dogs receiving halothane anesthesia and six of 12 dogs receiving N_2O sedation were prepared for modified open ventriculocisternal perfusion. Minute ventilation was set to maintain Pa_{CO_2} at about 20 mmHg. Mock CSF was infused into the ventricle, and the mixture of mock and native CSF was permitted to flow passively out of the cisterna magna through a short

TABLE 1. Initial $\dot{V}_f$ Values and Regression Equations for $\dot{V}_f$ during Hypocapnia (Present Study) and Initial $\dot{V}_f$ Values during Normocapnia (Previously Reported), μl/min, Mean ± SD

	N_2O (66%) in O_2 (halothane 0.15%) (n = 6)	Halothane (0.8%) and N_2O (66%) in O_2 (n = 6)
Hypocapnia		
Closed ventriculocisternal perfusion	48 ± 11	32 ± 9*
Open ventriculocisternal perfusion	49 ± 8	35 ± 10*
Normocapnia		
Closed ventriculocisternal perfusion†	44 ± 13	31 ± 12*
Open ventriculocisternal perfusion†	47 ± 14	33 ± 12*
Regression equations for hypocapnia		
Closed ventriculocisternal perfusion	46.9 − 0.07 (x) (r = 0.28)	33.8 − 0.05 (x) (r = 0.33)
Open ventriculocisternal perfusion	48.5 − 0.07 (x) (r = 0.37)	35.4 − 0.05 (x) (r = 0.32)

$\dot{V}_f$ = the rate of CSF production; x = time, min.
* Significantly different from N_2O (66%) in O_2 (halothane, 0.15%), $P < 0.05$.
† Previously reported values.[7,13]

length of tubing attached to the cisternal cannula. The infusion rate was controlled with a roller pump and gradually increased to 30 μl/min, while ventricular CSF pressure was continuously monitored. The open end of the cisternal outflow tubing was placed at the same height as the CSF level that was present in the cisternal and ventricular cannulae before perfusion was begun. This arrangement did not alter CSF pressure from the value normally occurring in the intact animal, because the height of the open end of the outflow tubing determines CSF pressure during open ventriculocisternal perfusion. Successful ventriculocisternal perfusion was indicated by outflow of labeled CSF from the cisternal cannula with no increase in ventricular CSF pressure above pre-perfusion values. This initial period of open ventriculocisternal perfusion allowed for equilibration of labeled mock CSF with native CSF in the intracranial and cisternal CSF spaces of the dog. Details of this technique were previously reported.[10]

T_{eq} was defined as the time when measured tracer concentrations in three consecutive samples of cisternal outflow (collection time = 4–6 min per sample) agreed within 2%. Concentrations of Blue Dextran in cisternal outflow samples and samples of the labeled mock CSF being perfused into the ventricle were determined using light absorbence at 620 nm on a Beckman DU-2 Spectrophotometer (Beckman Instruments, Inc., Fullerton, CA) (fitted with a Gilford absorbence indicator, Gilford Instrument Laboratories, Inc., Oberlin, OH). $\dot{V}_f$ and the rate of reabsorption ($\dot{V}_a$) were determined at the time of tracer equilibration and at 45, 90, 135, and 180 min following tracer equilibration. At each time period, three consecutive samples of cisternal outflow were collected (collection time = 4–6 min per sample) for determinations of $\dot{V}_f$ and $\dot{V}_a$. $\dot{V}_f$ and $\dot{V}_a$ were calculated as previously described[11] according to the formulas of Heisey *et al.*[8] (Appendix). CSF pressure and systemic variables also were recorded at the time of tracer equilibration and at 45, 90, 135, and 180 min following tracer equilibration. VD_x was calculated as described above.

Statistical Analysis

Statistical comparisons within groups were made using repeated-measures analysis of variance, and comparisons between groups (including comparison of $\dot{V}_f$ values from the present study to previously reported values[7,13]) were made using one-way analysis of variance.[14] Where the calculated F value exceeded the critical value for the 0.05 probability level, the Student-Newman-Keuls' test was used to determine which differences were significant at $P < 0.05$.[15] The relationship between $\dot{V}_f$ or $\dot{V}_a$ and time was determined by linear regression analysis and computation of the correlation coefficient. The *t* statistic was used to determine whether the correlation coefficient was significant at $P < 0.05$.[16] Values are tabulated as mean ± SD.

Results

Both perfusion techniques yielded similar values for $\dot{V}_f$ (table 1). During hypocapnia and N_2O sedation, $\dot{V}_f$ was 48 ± 11 μl/min (mean ± SD, closed technique) and 49 ± 8 μl/min (modified open technique). During hypocapnia and halothane anesthesia, $\dot{V}_f$ was 32 ± 9 μl/min (closed technique) and 35 ± 10 μl/min (modified open technique), significantly lower than during N_2O sedation. $\dot{V}_f$ did not change significantly with time during either N_2O sedation or halothane anesthesia. T_{eq}, CSF pressure, and systemic variables were not significantly different between dogs examined during N_2O sedation and those examined during halothane anesthesia (table 2). Neither CSF pressure nor systemic variables changed significantly with time.

With closed perfusion, VD_x during halothane anesthesia, 6.10 ± 0.03 ml, was significantly lower than during N_2O sedation, 6.21 ± 0.07 ml. With modified open perfusion, $\dot{V}_a$ during halothane anesthesia was significantly lower than during N_2O sedation. VD_x values with N_2O sedation or halothane anesthesia during open perfusion were greater than respective VD_x values during closed perfusion. T_{eq} also was greater with open ventriculocisternal perfusion. In contrast, CSF pressure and systemic variables were similar during open ven-

TABLE 2. CSF Values and Systemic Variables at the Completion of Tracer Equilibration, Mean ± SD

	N_2O (66%) in O_2 (Halothane 0.15%)		Halothane (0.8%) and N_2O (66%) in O_2	
	Closed Perfusion, n = 6	Open Perfusion, n = 6	Closed Perfusion, n = 6	Open Perfusion, n = 6
$\dot{V}_a$ (μl/min)	—	26 ± 16	—	18 ± 11*
CSF pressure, intra-ventricular (cm H_2O)	8.0 ± 2.4	7.0 ± 1.8	7.8 ± 1.5	6.8 ± 2.0
VD_x (ml)	6.21 ± 0.07†	6.69 ± 0.27†	6.10 ± 0.03*†	6.59 ± 0.15†
T_{eq} (min)	130 ± 11†	157 ± 10†	126 ± 7†	155 ± 7†
CSF osmolality (mOsm/kg)	307 ± 20	304 ± 15	306 ± 19	308 ± 13
Perfusion rate of mock CSF (μl/min)	30 ± 1	30 ± 1	30 ± 1	30 ± 1
Pa_{O_2} (mmHg)	150 ± 27	163 ± 29	158 ± 25	166 ± 31
Pa_{CO_2} (mmHg)	21.9 ± 0.7	19.5 ± 1.6	21.0 ± 2.5	19.6 ± 1.4
*p*H	7.51 ± 0.05	7.53 ± 0.05	7.54 ± 0.05	7.56 ± 0.04
Bicarbonate (m Eq/l)	17.1 ± 1.8	17.0 ± 1.6	17.6 ± 1.2	17.2 ± 0.6
Hemoglobin (g/dl)	12.1 ± 2.0	13.1 ± 2.0	13.2 ± 1.7	12.9 ± 2.1
Mean arterial pressure (mmHg)	109 ± 7	113 ± 10	94 ± 13	101 ± 11
Heart rate (beats/min)	102 ± 11	103 ± 12	94 ± 9	93 ± 9
Temperature, nasopharyngeal (°C)	37.3 ± 0.3	37.1 ± 0.1	37.1 ± 0.2	37.0 ± 0.3

$\dot{V}_a$ = the rate of reabsorption of CSF; VD_x = the initial volume of distribution of the Blue Dextran tracer; T_{eq} = the time to equilibration of the tracer.

* Significantly different from N_2O (66%) in O_2 (halothane 0.15%), $P < 0.05$.

† Values during open ventriculocisternal perfusion significantly different from corresponding values using closed ventriculocisternal perfusion, $P < 0.05$.

triculocisternal perfusion to those during closed ventriculocisternal perfusion.

Discussion

In this study, $\dot{V}_f$ values during prolonged hypocapnia were similar to $\dot{V}_f$ values previously reported during normocapnia for both N_2O sedation or halothane anesthesia (table 1).[7,13] Values were similar whether determined by closed[7] or open[13] ventriculocisternal perfusion. These results indicate that prolonged hypocapnia does not reduce $\dot{V}_f$ and, therefore, reduction of $\dot{V}_f$ is not one of the causes of decreased CSF pressure during prolonged hypocapnia.

It should be noted that this conclusion is based on comparison of $\dot{V}_f$ values from this study to "historical controls," *e.g.*, previously reported $\dot{V}_f$ values for normocapnia.[7,13] Determination of normocapnic $\dot{V}_f$ values was not incorporated into the present study design, because normocapnic $\dot{V}_f$ values have been determined in many previous studies in this laboratory and were found to be highly reproducible.

The conclusion that hypocapnia does not reduce $\dot{V}_f$ is consistent with the results previously reported by Martins *et al.*[3] and Hochwald *et al.*,[4] but is in contrast to the acute effects of hypocapnia on $\dot{V}_f$ reported by others.[6,17] Previous studies by Heisey *et al.*[6] and Ames *et al.*[17] reported that, acutely (30–60 min), hypocapnia decreased $\dot{V}_f$ and hypercapnia increased $\dot{V}_f$. Several explanations were proposed to account for the acute effects of hypocapnia on $\dot{V}_f$. One explanation is that hypocapnia causes vasoconstriction and hypercapnia causes vasodilation of choroid plexus vessels.[6,17] $\dot{V}_f$ is altered because secretion of CSF varies directly with choroid plexus blood flow.[18] A second explanation relates to altered availability of CO_2 at the choroid plexus.[2] Diffusion of CO_2 into epithelial cells is necessary for formation of intracellular hydrogen (H^+) (*via* carbonic anhydrase) at the choroid plexus. In turn, H^+ is necessary for exchange with sodium (Na^+) so that Na^+ can enter the epithelial cell and be pumped across the secretory epithelium, allowing energy-dependent formation of CSF to occur. Lowering Pa_{CO_2} reduces intracellular H^+, creating a shortage of Na^+ at the energy-dependent pump which decreases CSF formation. A third explanation is that choroid plexus *p*H is altered.[2] A change of intracellular *p*H from optimum values impairs the metabolic processes necessary for the energy-dependent formation of CSF.

The present results also indicate that $\dot{V}_f$ during hypocapnia and halothane anesthesia is lower than during hypocapnia and N_2O sedation. These results are consistent with previous reports that, during normocapnia, halothane reduced $\dot{V}_f$ in both dogs[13] and cats.‡

In the present closed perfusion studies, CSF pressures during hypocapnia and either N_2O sedation or halothane anesthesia (8.0 ± 2.4 and 7.8 ± 1.5 cm H_2O) were

‡ Van Landingham KE, Maffeo CJ, Jackson H, Butler AB: Cerebrospinal fluid dynamics in the cat under halothane and pentobarbital anesthesia. Abstracts of Scientific Papers, Annual Meeting of the Society for Neuroscience, 1981, p 89

similar to CSF pressure previously reported during normocapnia and either N_2O sedation or halothane anesthesia (7.8 ± 0.8 and 7.5 ± 1.5 cm H_2O[7]) using closed perfusion. The similarity of CSF pressure during hypocapnia to that during normocapnia suggests that the reduction of CBV caused by hypocapnia was matched by an increase of CSF volume. This conclusion is supported by our observation that hypocapnia increased VD_x. In the present closed perfusion studies, VD_x values, 6.21 ± 0.07 and 6.10 ± 0.03 ml, respectively, for N_2O sedation and halothane anesthesia, were greater than those previously reported during normocapnia, 5.98 ± 0.07 and 5.86 ± 0.04 ml, respectively, for N_2O sedation and halothane anesthesia.[7]

The similarity of CSF pressure at hypocapnia and normocapnia also suggests that hypocapnia did not affect R_a. This conclusion is based on the principle that CSF pressure is determined by $\dot{V}_f$ and R_a.[18] If CSF pressure and $\dot{V}_f$ are unchanged, R_a also must be unchanged. The conclusion that hypocapnia does not alter R_a is supported by the observation that, in the present open perfusion studies, $\dot{V}_a$ during halothane anesthesia was similar to $\dot{V}_a$ values previously reported at similar CSF pressure during normocapnia and halothane anesthesia.[19]

CSF pressure is directly related to $\dot{V}_f$ and to R_a.[18] That, in the present study, CSF pressure during N_2O sedation was similar to that during halothane anesthesia, even though $\dot{V}_f$ was lower during halothane anesthesia than $\dot{V}_f$ during N_2O sedation, suggests that R_a was greater during halothane anesthesia than during N_2O sedation. This conclusion is consistent with a previous report that halothane anesthesia increased R_a during normocapnia.[19]

With both closed ventriculocisternal perfusion and with modified open ventriculocisternal perfusion, CSF pressure initially can be set at values that are usual for each animal. However, of these two perfusion techniques, only closed ventriculocisternal perfusion allows CSF pressure to vary with respiratory and cardiac activity and preserves neurogenic influences on $\dot{V}_f$.[20-22] Our observation that both perfusion techniques provided similar $\dot{V}_f$ values during prolonged hypocapnia and either N_2O sedation or halothane anesthesia suggests that preserving CSF pressure variations or neurogenic influences is not crucial to the determination of $\dot{V}_f$.

In summary, the results of this study indicate that prolonged hypocapnia does not reduce $\dot{V}_f$ during either N_2O sedation or halothane anesthesia, and, therefore, reduction of $\dot{V}_f$ is not a cause for decrease of CSF pressure during prolonged hypocapnia. Results obtained with closed ventriculocisternal perfusion were similar to those obtained with modified open ventriculocisternal perfusion. The results also suggest that hypocapnia-induced decrease of CBV was matched by an increase of CSF volume, that hypocapnia does not alter R_a, and that R_a is greater during halothane anesthesia than during N_2O sedation. These latter conclusions are supported by the data on CSF pressure, VD_x, and $\dot{V}_a$ observed here, and are consistent with previously reported values for CSF dynamics determined at normocapnia.[7,9,16,18]

Appendix

$\dot{V}_f$ was calculated according to the following formula:

$$\dot{V}_f = \dot{V}_i\left(\frac{C_i - C_o}{C_o}\right),$$

where $\dot{V}_f$ is the rate of CSF production, V_i is the inflow rate of the reference solution, C_i is the inflow concentration of the tracer substance, and C_o is the outflow concentration of the tracer substance.

VD_x was calculated according to the following formula:

$$VD_x = \frac{\sum_{o}^{n} [\dot{V}_iC_i - \dot{V}_oC_o - C_x\bar{C}_o(f)]\Delta t}{\bar{C}},$$

where VD_x is the volume of distribution of the tracer substance, $\dot{V}_o$ is the rate of outflow of mixed tracer-laden mock CSF and native CSF from the intracerebral and cisternal CSF spaces of the dog, C_x is the steady state clearance of $x = \dot{V}_iC_i - \dot{V}_oC_o/\bar{C}$, $\bar{C}_o(f)$ is C_o at steady state conditions, and $\bar{C}$ is the mean concentration of the tracer in the ventricular system $= C_o + 0.37\,(C_i - C_o)$, as stated by Pappenheimer *et al.*[23]

$\dot{V}_a$ was calculated according to the following formula:

$$\dot{V}_a = \frac{\dot{V}_iC_i - \dot{V}_oC_o}{C_o},$$

where $\dot{V}_a$ is the rate of reabsorption of CSF.

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