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ASSESSMENT OF CEREBROSPINAL FLUID COMPLIANCE AND OUTFLOW RESISTANCE: ANALYSIS OF STEADY-STATE RESPONSE TO SINUSOIDAL INPUT

John D. Charlton
Richard N. Johnson

Biomedical Engineering and Mathematics Curriculum

and

Nels E. Pederson
J. Douglas Mann

Department of Neurology
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Cerebrospinal fluid dynamics have been studied in the past by analyses of responses to bolus, constant rate or constant pressure inputs. In this study, we present a method for analyzing CSF pressure responses to sinusoidal variation in the infusion rate.

Infusion of artificial CSF into the cisterna magna of adult rats was modulated sinusoidally between 0 and 30 μl/min. The resulting sinusoidal variation in intracranial pressure was recorded on a strip chart recorder simultaneously with the infusion rate signal. The two signals were analyzed for peak-to-peak variation, mean value, and phase shift for input frequencies in the range of 0.0015 to 0.01 Hz (0.00942 to 0.0628 radians/sec). The system was analyzed at each mean infusion rate as a parallel resistance and compliance with a first order linear model. The resistance to CSF outlfow was determined as the change in mean steady-state pressure divided by the change in mean infusion rate. The compliance was then obtained from the frequency dependent phase shift between input and output using the first-order linear model. Resistance values were lower for higher average infusion rates consistent with our previous work, while compliance remained constant over the measured pressure range.

Keywords *— Sinusoidal, CSF, Cerebrospinal fluid, System identification.*

Address correspondence to John D. Charlton, Biomedical Engineering, 152 MacNider Hall 202H, University of North Carolina, Chapel Hill, NC 27514.

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INTRODUCTION

Major efforts at identification of the fluid mechanical parameters of the cerebrospinal fluid (CSF) system have employed constant rate infusion of artificial CSF (3,4), bolus injection of fluid (5,6), or feedback control of CSF pressure by automatic adjustment of the infusion rate (2,8,9). We have previously employed a nonlinear mathematical model of the CSF system assuming a logarithmic relationship between constant infusion rate and steady-state CSF pressure (3). In that model, resistance to CSF absorption and CSF compliance are functions of CSF pressure and endogenous CSF formation rate is assumed to be small in comparision to the constant infusion rate and to decrease linearly with increasing CSF pressure. Marmarou et al. (5,6) have employed the bolus injection method of CSF infusion with a nonlinear mathematical analysis based on different assumptions. These assumptions were a constant CSF absorption resistance and an exponential relationship between the bolus volume injected and the resulting peak CSF pressure attained (5,6). Although these two methods are based on different mathematical models derived from different basic assumptions, we have shown that the *average* resistance to CSF absorption calculated by our method (3) is within 10% of the constant resistance calculated by Marmarou et al. (5,6). Sullivan et al. (10) found a discrepancy between the values of resistance to CSF absorption calculated from the bolus injection method and the constant infusion method. However, they assumed a linear relationship between the constant infusion rate and the CSF pressure response.

While resistance to CSF absorption calculated by constant infusion and bolus injection methods may be in approximate agreement (3), the compliance calculations are not in agreement. Marmarou et al. (5) assumed a compliance inversely proportional to CSF pressure and defined the constant of proportionality as the pressure–volume index (PVI) (5). On the other hand, using a least-squares method, and our nonlinear model, we have previously found that the compliance increased with constant infusion rate (i.e., increasing CSF pressure) (3). In addition, the results using the bolus injection/pressure–volume index method have been conflicting as to the nature of CSF compliance. Some investigators have found that the pressure–volume response is exponential (5,6,9) while others have found a linear relationship (11). Another approach has been to use the arterial blood pressure pulse as an input and the intracranial pressure (P) as the output and to determine the transfer function between the two (1). Although this latter approach offers an interesting alternative to the existing methods, the transfer function between arterial pulsations and CSF pressure only tests the characteristics of the system for pressure input with frequencies contained in the arterial pressure signal. Thus, it may not give valid characteristics of the system for lower frequency variations in CSF formation and resistance to CSF absorption. In the present experiments we have used sinusoidal modulation of the infusion rate and

a piecewise linear model of the CSF system to analyze resistance to CSF absorption and CSF system compliance over different ranges of infusions and pressures.

EXPERIMENTAL METHODS

Adult albino rats of either sex weighing between 300 and 600 grams were anesthetized with halothane (1% in 99% O_2), intubated, artificially ventilated, and paralyzed with pancuronium (0.5mg/kg/hr. i.v.). Arterial blood pressure was monitored on a Grass polygraph via a femoral arterial catheter to insure that the preparation was stable. Data were not used in the analysis when mean arterial blood pressure was outside the range of 80 to 100 mmHg or when heart rate changed by more than 50 beats per minute during data collection. Arterial blood gases were also monitored and maintained in a physiologic range. A 19 gauge needle was inserted through the dura into the cisterna magna and used for infusion of artificial CSF and monitoring of intracranial pressure (P) as we have described in previous work (4).

A Wavetek waveform generator was used to generate sinusoidal signals in the frequency range from 0.0015 Hz to 0.01 Hz (0.00942 to 0.0628 rad/sec). The sinusoid thus generated was offset by a constant voltage source and calibrated to modulate the infusion rate of artificial CSF between predetermined limits (0 to 20 or 10 to 30 μl/min) (Fig. 1).

A Sage syringe pump modified for external voltage control was employed for the artificial CSF infusion. The frequency response of the pump was tested with a step increase in input voltage. The output of the 5 cc syringe used in the test was measured as the pressure drop across a 25 gauge needle connected to the syringe. This pressure signal was measured with a National Semiconductor pressure transducer and displayed on a strip chart along with the input signal. The time delay between the input signal and the output pressure change was measured directly from the strip chart as 0.15 sec. The time constant was determined to be 1.64 sec by measuring the time the output took to reach 63% of its final value. The resulting transfer function is:

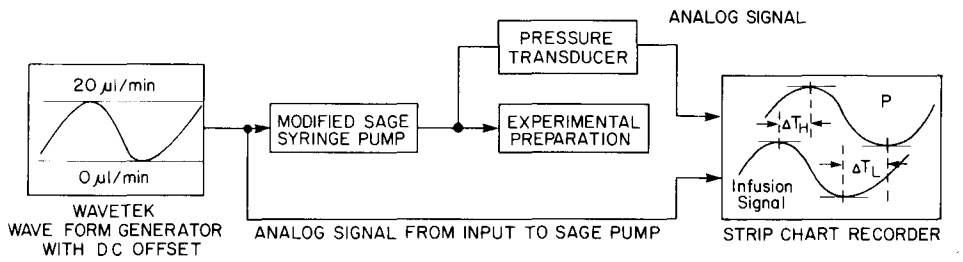

FIGURE 1. Experimental Apparatus. P—Intracranial pressure; ΔT_H—Phase lag at peak P; ΔT_L—Phase lag at trough P.

$$G_p(S) = \frac{K_p e^{-0.15s}}{1 + 0.61s}$$

where K_p is a constant relating input voltage to output flow (μl/min).

This transfer function can be approximated by K_p for frequencies below 0.1 radian/sec because at these frequencies $1 + 0.61j \approx 1$ and the phase contribution of the transport lag term $e^{-0.15s}$ is less than 1 degree in magnitude. Since the corner frequency of the CSF system is an order of magnitude lower than this, we used K_p to approximate the pump characteristics.

Intracranial pressure was monitored and displayed, along with the signal to the pump, on a polygraph (Figs. 1 and 3).

Data were collected when transient changes in the pressure were no longer observed and the output was a steady-state sinusoid with the same frequency as the input. This usually occurred after about five minutes of recording for a given input signal. The amplitude attenuation was then plotted as a function of frequency and used to determine the system time constant as described in the next section. The measured phase lag between the input infusion sinusoid and the output pressure sinusoid was also used to calculate the system time constant.

MATHMETICAL MODEL DEVELOPMENT

We modeled the CSF system with a piecewise linear first order transfer function derived from the nonlinear electric circuit analog we have employed previously (Fig. 2) (3). This piecewise linear approximation assumes that the endogenous CSF formation rate (Q_N), system compliance (C) and dynamic resistance (R_d) *do not change appreciably over the pressure range for a given sinusoidal infusion.* Since the superior sagittal sinus is part of the venous system, its pressure (P_{ss}, Fig. 2) is assumed to remain constant over the period of infusion. This assumption should be reasonable if the pressure range is not reached where occlusion of the venous outflow from the cranium occurs. Since only changes in pressure and flow are considered and the superior sagittal sinus pressure (P_{ss}, Fig. 2) is assumed constant, it has been neglected. This results in the following transfer function between the small signal input (Q_T*) and small signal output (P*):

$$(P^* / Q_T^*) = R_d / (R_d C s + 1), \tag{1}$$

where

$P^* = (P - \bar{P})$, $\bar{P}$ is the mean pressure (mmH_2O)
$Q_T^* = (Q_T - \bar{Q}_T)$, $\bar{Q}_T$ is the mean infusion rate (μl/min)

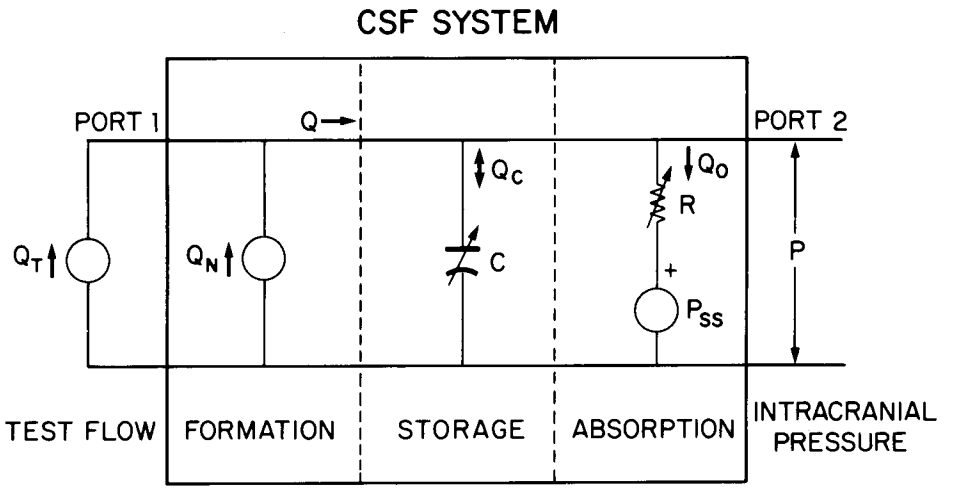

FIGURE 2. Electricial Curcuit Analog of The CSF System. Q_T—Test infusion; Q_N—Endogenous CSF formation rate; C—Compliance of CSF system; R—Resistance to CSF absorption; P_{ss}—Venous back pressure in the superior sagittal sinus; P—Intracranial pressure.

R_d = $P^*(t = \infty)/Q_T^*(t = \infty)$, $Q_T^*(t = \infty)$ = constant, dynamic resistance to CSF outflow from the CSF system into the venous system [$mmH_2O/(\mu l/min)$]

C = compliance of CSF compartment in $\mu l/mmH_2O$

s = the complex Laplace variable

Assuming steady-state conditions the "s" in the above equation can be replaced with "$j\omega$" (j is the imaginary number $\sqrt{-1}$) and the frequency dependent phase and magnitude can be calculated. The time constant ($\tau = R_d \times C$) is related to the phase shift as

$$\tau = R_d \times C = \tan(\phi) / \omega, \tag{2}$$

where

ϕ = phase shift in degrees

ω = angular frequency of the input sinusoid in radians/second.

The time constant (τ) can also be determined from a plot of magnitude of response versus frequency on log-log coordinates by the standard Bode technique (7). A third way of obtaining τ is from the transient response to a step increase in infusion rate. Tau (τ) is the "rise time" or the time after the step change in Q_T at which the pressure reaches 63% of its final or steady-state change. In the present study these three techniques were employed to calculate the system time constant (τ), and the results by each were compared. The dynamic resistance (R_d) was always calculated using the constant infusion technique and always for an increase in infusion rate from a steady-state resting level to a new steady-state

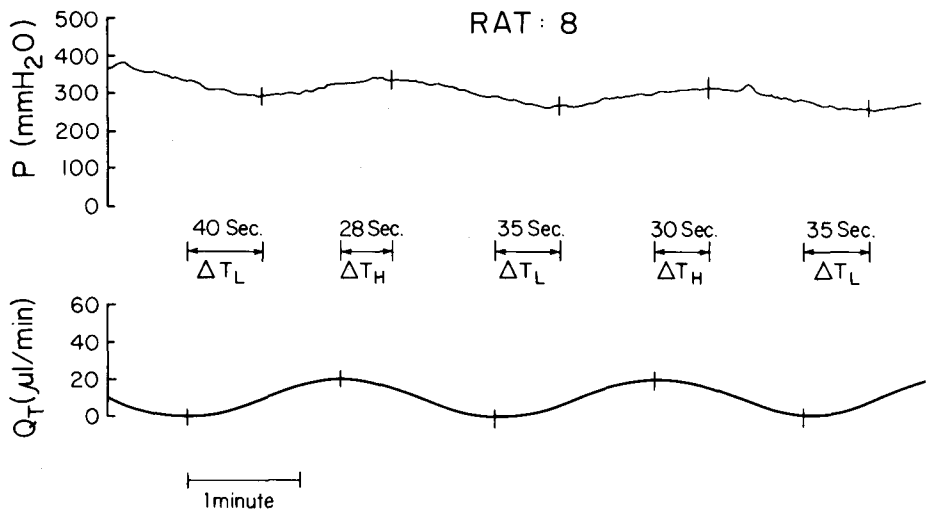

FIGURE 3. Typical Input/Output Wave Forms. P–Intracranial pressure; Q_T–Sinusoidal infusion rate; ΔT_H–Phase lag at peak P; ΔT_L phase lag at trough P.

resting level. The first value for R_d was obtained by changing the infusion rate from its initial level of 0μl/min with resting pressure P_0 to 10μl/min and waiting for the pressure to reach its steady state value, P_1. For this case $R_d = (P_1 - P_0)/(10\ \mu l/min - 0\mu l/min)$. The next value is obtained by starting at steady state pressure P_1 and increasing the infusion rate to 20 μl/min. The resulting new steady state pressure, P_2, is then used to obtain the new value $R_d = (P_2 - P_1)/(20\ \mu l/min - 10\ \mu l/min)$. For sinusoidal inputs R_d is determined just prior to sinusoidal infusion by a constant infusion at the trough rate to obtain the steady state pressure P_0 and then infusing at the peak rate to obtain the steady state peak pressure P_1. For a 0 to 20 μl/min infusion sinusoid, $R_d = (P_1 - P_0)/(20\ \mu l/min - 0\mu l/min)$.

The break frequency (ω_0) for the transfer function above (Eq. 1) is the frequency at which the magnitude is down 0.707 of the low frequency or steady-state value and the phase shift is 45°. This frequency can be obtained directly from the magnitude plot or calculated from the phase shift (ϕ) for a given input sinusoid by the equation,

$$\omega_0 = 1/\tau = \omega/\tan(\phi). \tag{3}$$

RESULTS

Data were collected for a total of thirteen rats and are presented in Tables 1, 2 and 3. The number of data points used in each calculation is indicated below the

mean and standard deviation for that calculation. The numbers of data points used in the different calculations are not the same since it was not always possible to collect data for all calculations in each experiment.

The intracranial pressure taken as the output of the system has a characteristic phase lag when compared to the input sinusoidal modulation of infusion (Q_T) into the CSF compartment (Fig. 3). Using the first order linear model discussed in the previous section, the system time constant was calculated both from the amplitude attenuation and the phase shift between input and output (Tables 1 and 2). The frequency dependent amplitude attenuation was plotted (Fig. 4) and the system time constant was determined graphically from the plot to fit the first-order linear model (Table 1). The phase lag was determined from the raw data (Fig. 3), converted to degrees, and was also used in the first order linear model to calculate the system time constant (Table 2). These two methods of obtaining the system time constant agreed well with each other within the margin of experimental error (Tables 1 and 2).

An independent calculation of the system time constant was obtained from the constant infusion runs by measuring τ as the rise time from a step increase in infusion rate for infusion rates between 0 and 30 μl/min (Table 3). The time constant appears longer at 10 μl/min for constant infusion (Table 3) than for the sinusoidal technique (Tables 1 and 2). However, using a t-test for means of populations this difference is not significant at the $p < .01$ level. Using the t-test and comparing all other combinations of population means for τ in Tables 1, 2 and 3 at comparable infusion rates revealed no significant differences at the $p < .01$ level. The dynamic resistance (R_d), calculated as discussed in the Methods, shows a characteristic decrease with increasing pressure consistent with previous results in our laboratory (Table 3) (3,4). This resistance (R_d) was divided into the time constant (τ) to obtain the system compliance ($C = \tau / R_d$) according to the first order linear model (Eq. 1) for which $\tau = R_dC$. This decrease in resistance accounts for a decrease in the time constant with an increase in pressure (or infusion rate). The compliance calculated with these three methods

TABLE 1. Sinusoidal Input: Magnitude Data and Calculations.[a]

Sinusoidal Infusion Rate (Q_T[b], peak-to-peak) (μl/min)	Mean Intracranial Pressure (mm H_2O)	Dynamic Resistance (R_d)[c] [mm H_2O/(μl/min)]	Break Freqency (ω_o)[d](rad/sec)	Time Constant (τ)[e] (seconds)	Compliance (C)[f] (μl/mm H_2O)
0 to 20	308 ± 90.3 (n = 8)	14.9 ± 4.60 (n = 10)	.013 ± .0041 (n = 5)	90 ± 38.8 (n = 5)	0.1 ± .04 (n = 5)
10 to 30	395 ± 54.5 (n = 8)	8.7 ± 1.91 (n = 11)	.019 ± .0053 (n = 7)	59 ± 21.8 (n = 7)	0.1 ± .02 (n = 7)

[a]Mean ± SD for all values except Q_T[b].
[b]Sinusoidal frequency was from 0.0015Hz to 0.01Hz.
[c]R_d = steady-state change in pressure/increase in constant infusion rate.
[d]ω_o = obtained graphically from magnitude versus frequency plot.
[e]$\tau = R_d \times C = 1/\omega_o$.
[f]$C = \tau/R_d$.

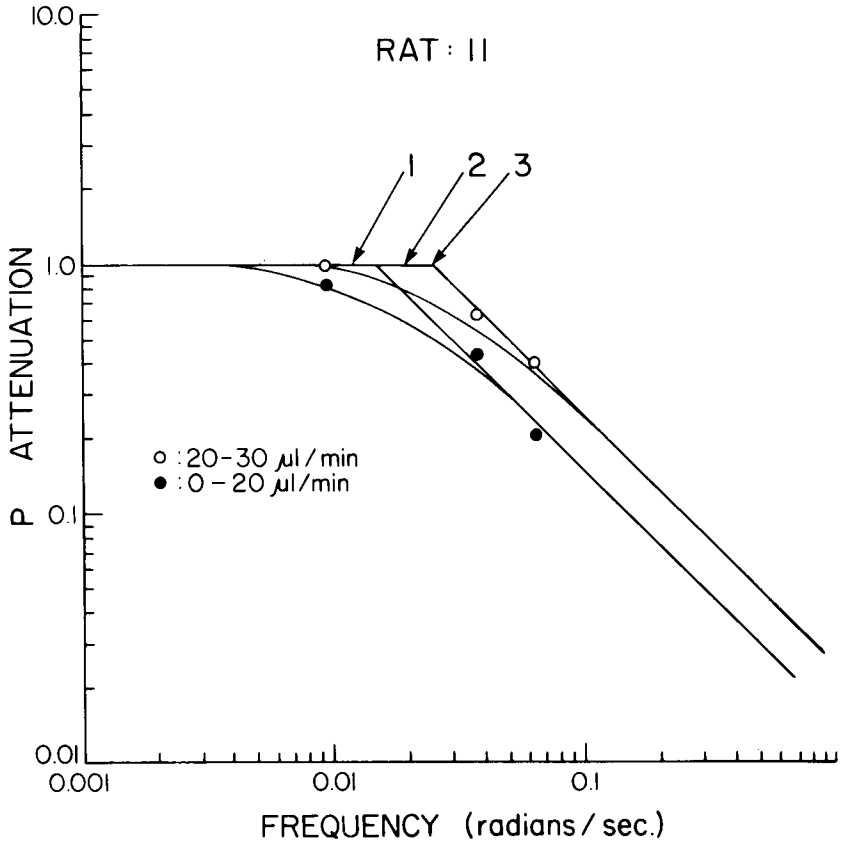

FIGURE 4. Relative Magnitude of Changes in Intracranial Pressure with Frequency. P—Intracranial pressure; 1—Break frequency calculated from trough phase lag for 0 to 20 µl/min infusion sinusoid; 2—Break frequency calculated from peak phase lag for 0 to 20 µl/min infusion sinusoid; 3—Break frequency calculated from mean phase lag for 10 to 30 µl/min sinusoid.

remains constant over the pressure range employed in the present study (i.e., 150 to 500 mmH_2O; Tables 1, 2 and 3).

In animals where large pressure changes occurred with the sinusoidal input, a difference was observed in the phase shift at high pressures and at low pressures. The time lag to peak output pressure was, in some cases, shorter for the half cycle where pressure was high (ΔT_H, Fig. 3) than for the half cycle where pressure was low (ΔT_H, Fig. 3). Thus a time lag at the high pressure half cycle (ΔT_H, Fig. 3) could be used to calculate one phase shift and the time lag at the low pressure half cycle (ΔT_L, Fig. 3) could be used to determine a second phase shift. In order to compare the calculations of the time constant using the phase shift and the magnitude plot techniques, the break frequency (ω_0, Eq. 3) was determined from the phase shift data and indicated on the magnitude plot in radians/second (Fig. 4; points 1, 2, and 3). The break frequency for the low pressure half cycle was lower than that for the magnitude plot (Fig. 4, point 1) and the break frequency for the higher pressure half cycle was higher than for the magnitude plot (Fig. 4,

TABLE 2. Sinusoidal Input: Phase Data and Calculations. [a]

Sinusoidal Infusion Rate (Q_T[b], peak-to-peak) (μl/min)	Mean Intracranial Pressure (mm H_2O)	Dynamic Resistance (R_d)[c] [mm H_2O/(μl/min)]	Break Freqency (ω_o)[d](rad/sec)	Time Constant (τ)[e] (seconds)	Compliance (C)[f] (μl/mm H_2O)
0 to 20	264 ± 64.0 (n = 7)	14.2 ± 4.34 (n = 9)	.011 ± .0054 (n = 7)	113 ± 62.2 (n = 7)	0.1 ± .08 (n = 7)
10 to 30	373 ± 79.5 (n = 9)	9.1 ± 1.87 (n = 9)	.020 ± .0096 (n = 9)	58 ± 21.3 (n = 9)	0.1 ± .03 (n = 9)

[a]Mean ± SD for all values except Q_T[b].
[b]Sinusoidal frequency was from 0.001Hz to 0.01Hz.
[c]R_d = steady-state change in pressure/increase in constant infusion rate.
[d]$\omega_o = 1/\tau = 2\pi f/(\tan\phi)$ where f is the input sinusoidal frequency.
[e]$\tau = R_d \times C = (\tan\phi)/2\pi f$.
[f]$C = \tau/R_d$.

point 2). For the high infusion sinusoid (10 to 30 μl/min peak-to-peak), the break frequency from the magnitude plot was the same as that calculated from the phase shift (Fig. 4, point 3). The phase shift was not different in the low and high pressure half-cycle, so only one break frequency was calculated from the phase data for the high infusion sinusoid in this animal (Fig. 4, point 3). This difference in phase shift for high and low pressures results from nonlinearities in the system and indicates the linear assumption will be violated to some degree in animals where large pressure changes occur.

TABLE 3. Constant Rate CSF Infusion Data and Calculations. [a]

Constant Infusion Rate (Q_T)[b] (μl/min)	Mean Intracranial Pressure (mm H_2O)	Dynamic Resistance (R_d)[c] [mm H_2O/(μl/min)]	Break Freqency (ω_o)[d](rad/sec)	Time Constant (τ)[e] (seconds)	Compliance (C)[f] (μl/mm H_2O)
0	83 ± 34.0 (n = 10)	—	—	—	—
10	254 ± 76.0 (n = 10)	17.5 ± 7.52 (n = 10)	.004 ± .0021 (n = 8)	292 ± 151.8 (n = 8)	.27 ± .172 (n = 8)
20	398 ± 125.0 (n = 10)	13.7 ± 6.18 (n = 10)	.016 ± .0071 (n = 9)	79 ± 48.3 (n = 9)	.12 ± .078 (n = 9)
30	410 ± 71.0 (n = 8)	6.8 ± 3.18 (n = 8)	.016 ± .0095 (n = 6)	90 ± 62.3 (n = 6)	.20 ± .130 (n = 6)

[a]Mean ± SD.
[b]Infusion rate was progressively increased in 10 μl/min steps from 0 to 30 μl/min.
[c]R_d = steady-state change in pressure/increase in constant infusion rate.
[d]$\omega_o = 1/\tau$.
[e]τ was obtained as 63% time response from strip chart.
[f]$C = \tau/R_d$.

DISCUSSION

The three methods we have used to calculate the CSF system time constant and break frequency, based on a piecewise linear model of this system with sinusoidal and constant input, all produce consistent results. This suggests that the electric circuit analog of Fig. 2 previously employed by our group (3) using a nonlinear mathematical model and by Marmarou et al. (6) using a different mathematical formulation is a valid representation of the CSF system. The peak-to-peak amplitude of the infusion sinusoids were large enough in some cases to show nonlinearities in the system manifesting as phase lag differences between the input and output for the peak and trough of the pressure sine wave. Since we obtained the average time constant over the pressure range, these nonlinear effects were judged to be minor. In addition, having a relatively large pressure change aided in determining the peak and trough pressures.

There is approximate agreement between the results of this technique and the least squares technique we have employed previously for the calculation of compliance (3). Using that technique the compliance was seen to increase with infusion rate. The results of the present study using sinusoidal inputs indicate that the compliance remains constant for the infusion rates employed. The discrepancy may result in the present study from using the average of the dynamic resistance over the infusion range, whereas in the previous work the least squares analysis incorporated a nonlinear pressure/absorption relationship at each pressure over the range of the response. Utilization of smaller infusion sinusoids and computerized spectral analysis of the CSF pressure waveform should clarify this discrepancy in the future.

The constant compliance observation was not expected initially and is not in agreement with the results of others (5,6) who have found compliance to decrease with pressure. This is possibly due to the fact that others have assumed a constant resistance over the entire pressure range. If the compliance is indeed constant over this pressure range, then the decrease in dynamic resistance would account for the decrease in the time constant with pressure observed in all of the techniques employed in the present study. This decrease in the system time constant or response time with increasing intracranial pressure means that the system responds more rapidly to CSF volume changes at higher pressures. Since the compliance of the CSF system is a result of displacing blood from the venous and, to a lesser extent, the arterial system of the cranium, this compliance should be related to the geometry of the venous blood vessels. A constant compliance suggests that the geometry of these vessels does not change significantly in the physiological range of pressures we have employed. This is reasonable from a functional point of view since one would not expect the cerebral blood volume to change appreciably over the normal physiological range of CSF pressure.

Previous work employing frequency response techniques has looked at higher frequency ranges than the present study (1). We are presently preparing to use pseudo-random and sweep sinusoidal modulation of the pump signal to avoid the

need to stimulate the system at discrete frequencies. This will avoid errors which may occur due to changes in the system over the time used to stimulate at discrete sinusoidal rates.

This approach to CSF parameter identification offers a viable alternative to the methods presently in use by basing the parameter estimation on a continuous response rather than a transient response to a steady infusion or a bolus injection. This initial study indicates that sinusoidal analysis is appropriate for the CSF system and that future studies using sweep sinusoids or band limited white-noise may aid in refining the estimates of CSF compliance and absorption resistance as well as further clarifying the nature of the relationship of these parameters to CSF pressure.

REFERENCES

1. Chopp, M. and H.D. Portnoy. Systems analysis of intracranial pressure, comparison with volume-pressure test and CSF-pulse amplitude analysis. *J. Neurosurg.* 53:516-527, 1980.
2. Ekstedt, J. CSF hydrodynamic studies in man. 1. Method of constant pressure CSF infusion. *J. Neurol. Neurosurg. Psychiatry.* 40:105-119, 1977.
3. Johnson, R.N., C.J. Maffeo, J.D. Mann, A.B. Butler, and N.H. Bass. Intracranial pressure regulation: A comparative model of cerebrospinal fluid systems. T.-I.-T. *J. Life Sci.* 8:79-92, 1978.
4. Mann, J.D., A.B. Butler, J.E. Rosenthal, C.J. Maffeo, R.N. Johnson, and N.H. Bass. Regulation of intracranial pressure in rat, dog, and man. *Ann. Neurol.* 3:156-165, 1978.
5. Marmarou, A., K. Shulman, and J. LaMorgese. Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system. *J. Neurosurg.* 43:523-534, 1975.
6. Marmarou, A., K. Shulman, and R.M. Rosende. A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. *J. Neurosurg.* 48:332-344, 1978.
7. Melsa, J.L. and D.G. Schultz. *Linear Control Systems* New York: McGraw-Hill, 1969, pp. 224-237.
8. Portnoy, H.D. and P.D. Croissant. A practical method for measuring hydrodynamics of cerebrospinal fluid. *Surg. Neurol.* 5:273-277, 1976.
9. Sklar, F.H., C.W. Beyer, Jr., and W.K. Clark. Physiological features of the pressure-volume function of brain elasticity in man. *J. Neurosurg.* 53:166-172, 1980.
10. Sullivan, H.G., J.D. Miller, R.L. Griffith, III, W. Carter, Jr., and S. Rucker. Bolus versus steady-state infusion for determination of CSF outflow resistance. *Ann. Neurol.* 5:228-238, 1979.
11. Wilkinson, H.A., S. Rosenfeld, D. Denherder, and R. Bronson. The linearity of the volume/pressure response during intracranial pressure "reserve" testing. *J. Neurol. Neurosurg. Psychiatry.* 44:23-28, 1981.