# Review Article

## Cerebrospinal Fluid Dynamics Study: Applications in Clinical Practice

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## Abstract

The study of cerebrospinal fluid (CSF) dynamics is an important, yet, less well-known field. It has many important clinical applications, which include the disorders of CSF absorption. The methods of CSF dynamics measurement include Constant flow method, Constant pressure method, Bolus injection method, Radio-isotope dilution method, Phase contrast magnetic resonance imaging (MRI). The bolus lumbar injection method which has been improvised by the author is very useful for routine clinical application. The CSF dynamics study is very useful in the diagnosis and planning of treatment in normal pressure hydrocephalus, post-meningitic hydrocephalus, post-traumatic hydrocephalus and idiopathic intracranial hypertension.

Key words : Cerebrospinal fluid dynamics; Bolus lumbar injection method; Diagnosis of normal pressure hydrocephalus.

## Introduction

The study of cerebrospinal fluid (CSF) physiology is an interesting and under-explored field. Disorders of CSF absorption like normal pressure hydrocephalus (NPH), post-meningitic hydrocephalus, post-traumatic hydrocephalus, idiopathic intracranial hypertension (IIH), etc., often pose a challenge in diagnosis and management decisions. The study of CSF dynamics helps in the diagnosis and planning treatment of these disorders.

## Applied anatomy and physiology

The rate of CSF formation in humans is about 0.3–0.4 ml /min (about 500 ml day). Total CSF volume is 90–150 ml in adults. Potential sites of CSF formation include the choroid plexus, parenchyma of the brain and the spinal cord, and ependymal lining of the ventricles[1]. The fluid formed in the lateral ventricles escapes by the foramen of Monro into the third ventricle and then via the aqueduct into the fourth ventricle. From the fourth ventricle the fluid enters the subarachnoid spaces through the median foramen of Magendie and the two lateral foramina of Luschka. The absorption of the cerebrospinal fluid is a dual process. It is mainly through the arachnoid villi into the dural sinuses, and also through the perineural lymphatics (around ophthalmic, optic and vagal nerves) and via the capillary bed of the CNS[2].

There are two components in CSF circulation: (i) bulk flow (circulation) and (ii) pulsatile flow (back and forth motion). In bulk flow, CSF is produced by choroid plexus and absorbed by arachnoid granulations. The force, which provides CSF movement from the ventricular system to arachnoid granulation and CSF absorption, is caused by a hydrostatic pressure gradient between the site of its formation (slightly high pressure) and its site of absorption (slightly low pressure). In pulsatile flow, movement of the CSF is pulsatile and results from pulsations related to cardiac cycle of the choroid plexus and the subarachnoid portion of the cerebral arteries[3].

The CSF outflow resistance (Rout) is the most important parameter measured in the CSF dynamics study. Rout is the reciprocal of conductance (Cout) and reflects the CSF absorption at the arachnoidal villi. Rout measurement helps in the diagnosis and planning treatment of clinical disorders of CSF absorption.

## Methods of Rout measurement

There are various methods of measuring Rout. The most important among them are: 1) Constant flow infusion (Katzman) method, 2) Constant pressure (servo-controlled) infusion method) and 3) Bolus injection (Marmarou) method. Radio-isotope dilution method and Phase contrast MRI (PC MRI) are also used in qualitative and quantitative study of CSF dynamics.

## Constant flow infusion (Katzman) Method

The method of constant flow infusion was first introduced as a clinical tool in 1970 by Katzman and Hussey[4]. The method was later modified by others. Artificial CSF/saline is infused, usually through a lumbar or intraventricular needle, into the CSF space at a constant rate, and the corresponding rise in ICP/CSF pressure is registered and analysed. When ICP reaches

a steady state level (plateau), where the external input of artificial CSF added to the formation rate is equal to the absorption rate, the outflow conductance is given by Cout = Iext/ Pplateau – Pr where Iext is the rate of external infusion, Pplateau is the mean ICP on the new steady state plateau, and Pr is the resting pressure prior to infusion.

## Constant pressure infusion method

The method of constant pressure infusion was clinically introduced by Ekstedt in 1977. When using the constant pressure infusion method, ICP is regulated to specific pressure levels, and the inflow of artificial CSF/saline needed to maintain that pressure is measured. This can be achieved with a peristaltic pump and a regulating system. Several predetermined pressure levels are employed, and on each pressure level mean ICP and net flow is determined. The flow is linearly dependent on ICP (given that the dural sinus pressure and the formation rate of CSF are constant), and thus Cout is assessed as the slope of the linear regression between flow and corresponding mean pressures[5,6].

## Bolus injection (Marmarou) method

The bolus infusion test is based on a fast injection of a small volume of artificial CSF/saline and the study of the CSF pressure response to that injection developed by Marmarou[7,8]. The Madras Institute of Neurology (MIN) method devised by the author, is an improvised Marmarou's bolus lumbar injection method, using saline manometer made with easily available bed side material[9]. A saline manometer (if not readily available) is made using an intravenous set mounted on a meter scale and was filled with saline up to 11 cm of water with zero level corresponding to the level of the spine. Lumbar puncture is performed with 20G spinal needle and connected to the saline manometer through a three-way adapter. After the saline column stabilises the opening pressure (Po) is noted. A known volume of saline (rV), usually 5 or 10 ml is injected into the subarachnoid space through the three-way port at the rate of 1 ml/second. The peak pressure (Pp) reached after the bolus injection is noted. Once the saline column in the manometer starts falling gradually, after a fixed time ('t' in minutes), the pressure recording in the manometer (Pt) is noted. The CSF outflow resistance (Rout) is calculated using two step formula described by Marmarou[7,8].

**I step:** Pressure Volume Index (PVI) = rV/ log (Pp/Po)

**II step:** Rout = t.Po / PVI [log Pt (Pp - Po) / Pp (Pt - Po)] cm of water/ml/min.

This is converted into mm Hg/ml/min (cm of water/ml/min divided by 1.36).

## Radio-isotope dilution method

This consists of injecting a radio-nuclide (I125,131, Tc99m) tagged to albumin or contrast agent into lumbar subarachnoid space and recording the radioactivity at various time intervals[10]. This is rarely used in clinical practice in the present day.

## Phase contrast MRI

The PC MRI generates signal contrast between flowing and stationary nuclei by sensitising the phase of the transverse magnetisation to the velocity of motion. Before PC MRI data are acquired, the anticipated maximum CSF flow velocity must be entered into the pulse sequence protocol (velocity encoding (VENC). To obtain the optimal signal, the CSF flow velocity should be the same as, or slightly less than, the selected VENC. The mean VENC value is 5–8 cm/s for standard CSF flow imaging. In normal pressure hydrocephalus, significantly higher VENC values (20–25 cm/s) should be chosen owing to hyperdynamic CSF flow within the cerebral aqueduct. Quantitative CSF velocity and qualitative flow information can be obtained in 8 to 10 additional minutes in connection with routine MRI[11].

The constant flow infusion and the constant pressure infusion methods, though accurate, are difficult to perform in the routine clinical setting and are time consuming. Radio-isotope method is not widely used at present. The PC MRI is not yet widely and routinely available. The MIN method of bolus lumbar injection is a very simple bedside test, which can be performed with easily available equipment and has a good accuracy and useful for routine clinical application.

## Clinical Applications

Communicating hydrocephalus is a fairly common clinical problem. This is due to a defect in the CSF absorption, which is mainly in the arachnoidal villi. The causes of communicating hydrocephalus are varied. The commonest of them are normal pressure hydrocephalus (NPH), post-meningitic hydrocephalus and post-traumatic hydrocephalus. All these situations may be mimicked by atrophic ventriculomegaly, either due to age related, post traumatic or post-meningitic causes. This might confuse the neurosurgeon in the decision making regarding shunt. Hence, in addition to the clinical and radiological parameters which may be dubious, there is a need for a fool proof investigative tool to determine the indications for shunt in these patients. A defect in the CSF absorption results in early increase in CSF outflow resistance. The increase in Rout precedes the clinical and radiological manifestations in patients with communicating hydrocephalus. The increase in Rout also often precedes the increase in intracranial pressure or subarachnoid CSF pressure as determined by measuring the opening pressure (Po) by lumbar puncture. Hence the measurement of Rout is likely to help in the early diagnosis of patients suitable for shunt in communicating hydrocephalus. The normal value of Rout in Indian population ranges from 3.82 to 9.7 mm Hg/ml/min, with a mean of 6.09 mm Hg/ml/min11. Rout value of 18 mm Hg/ml/min is kept as threshold for diagnosis and predicting good outcome following shunting in NPH[12,13]. Similarly elevated Rout is also helpful in the diagnosis and predicting good outcome following shunt in post-meningitic and post-traumatic hydrocephalus[9].

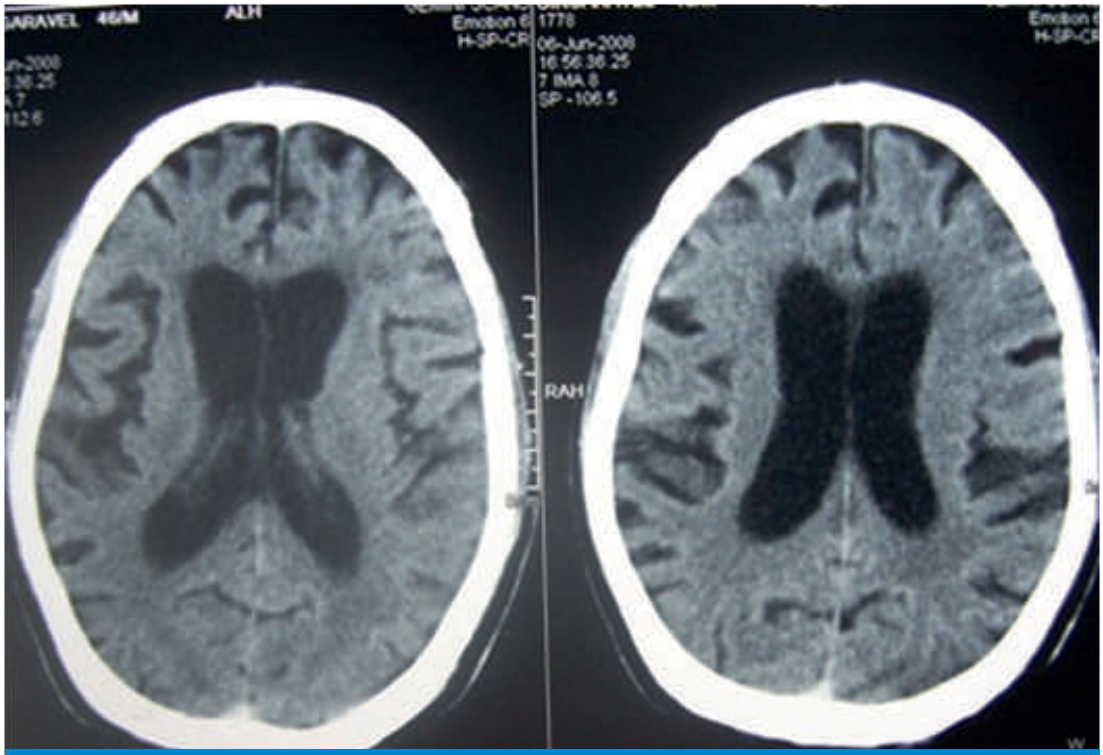


Fig 1:

**Idiopathic intracranial hypertension (IIH)**, also known as benign intracranial hypertension and pseudotumour cerebri, is another clinical condition due to derangement of CSF absorption. This condition also poses diagnostic problem, as it may be mimicked by other conditions. Rout is grossly elevated in IIH. Single measurement of opening pressure after lumbar puncture is not a very reliable yardstick in the diagnosis of IIH. Hence Rout measurement is very useful in the establishment of diagnosis of IIH[9,14].

## Clinical Vignette

A 45-year-old man was admitted with history of difficulty in walking and memory disturbances since 8 months. Neurological examination revealed slow gait with gait ataxia and moderate dementia with normal bladder function.

CT Brain (Fig.1) showed ventriculomegaly without periventricular lucency and some degree of cortical atrophy. The differential diagnosis in this patient would be either NPH or Alzheimer's dementia, since the clinical and CT pictures were not clear cut. The treatment and prognosis are completely different in both these conditions and hence precise diagnosis is mandatory. It is in such a situation that the CSF dynamics study is of immense help. CSF dynamics study (Bolus lumbar injection – MIN method) was performed in this patient, which showed opening pressure (Po) of 17cms of $H_2O$, which is only mild increase and not very conclusive. But CSF outflow resistance (Rout) measurement showed a value of 21.97 mm Hg/ml/min, which is an enormous increase. This conclusively established the diagnosis of NPH and the patient underwent ventriculo-peritoneal shunt surgery. He started showing very good clinical improvement in 10 days and near normal gait and memory at the time of discharge. This is an example to show the value of CSF dynamics study in establishing the diagnosis of an eminently treatable condition, namely, NPH.

## Conclusion

The field of CSF dynamics study is fascinating. The MIN bolus lumbar injection method is a reliable, simple method of measurement of Rout, which can be used for routine bedside application. Rout measurement is very useful in establishing the diagnosis and planning treatment in the various disorders of CSF absorption, namely, NPH, post-meningitic hydrocephalus, post-traumatic hydrocephalus and IIH.

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**EZH2 Makes it Easy**

EZH2 is an enzyme (Histone-lysine N-methyltransferase) that is encoded by the EZH2 gene in humans. It directly controls the expression of some 1200 genes. In a new study done at the University of Illinois, the researchers used bio-informatics techniques to show that the level of expression of these genes correlated with biological behaviour (aggressiveness) of breast cancer. In the study published online in Molecular and Cellular Biology (Molecular and Cellular Biology, 2013; DOI: 10.1128/MCB.00426-13), the researchers altered the expression EZH2 gene in breast cancer cell lines with small molecule RNA inhibitors. Depending on the degree of inhibition, the level of expression of controlled genes varied and allowed the researchers to develop an analysis pipeline that would prove useful in stratifying breast cancer patients based on aggressiveness. The authors feel that EZH2 may make it easy to predict the prognosis in breast cancer and also in deciding therapy. The small molecule RNA inhibitor used in this study has the potential to become a therapeutic agent.

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