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# Cerebrospinal Fluid Flow Parameters in Normal Subjects above 40 Years of Age

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## Abstract

**Background** Cerebrospinal fluid (CSF) flow is altered in many conditions like normal pressure hydrocephalus (NPH), aqueduct stenosis, or Chiari malformation. It is very important to know the normal CSF flow parameters for properly diagnosing these conditions. No data on CSF flow parameters of the Indian population are available. Hence, this study was undertaken to generate normative CSF flow parameters in the Indian population.

**Aim** Our aim was to estimate normal CSF flow parameters across the cerebral aqueduct in Indian subjects over 40 years of age.

**Settings and Design** This observational study was done in the tertiary care institute on subjects undergoing magnetic resonance imaging (MRI) for indications like headache and having normal MRI.

**Methods** Phase-contrast quantitative flow sequence was done in 100 subjects perpendicular to the cerebral aqueduct on 3.0T MRI (Discovery 750w with GEM suit, GE, Milwaukee, WI, United States) using a dedicated 32-channel head coil with 10 cm/s velocity encoding. The region of interest was kept at the cerebral aqueduct in cross-section. The inbuilt software calculated flow-time and velocity-time graphs and calculated peak systolic velocity (PSV), peak diastolic velocity (PDV), systolic flow (SF), and diastolic flow (DF). Stroke volume (SV) was calculated by averaging systolic and DFs. $p$-Value $< 0.05$ was considered significant.

**Results** Mean age was $53.72 \pm 10.53$ (40–78) years with 41 males and 59 females. PSV, PDV, SF, DF, and SV all showed a significant linear correlation with age with $p$-values of 0.001, 0.004, 0.009, $<0.001$, and $<0.001$, respectively. Only PDV ($p = 0.035$) and DF ($p = 0.045$) varied significantly with sex, values being higher in males.

**Conclusion** All five CSF flow parameters studied vary positively with age, and this variation is linear. Normal decadal median values calculated for these parameters can act as baseline values for the local population and help in defining conditions like NPH.

**Keywords**
- CSF flow
- phase-contrast quantitative flow sequence
- stroke volume

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## Introduction

Cerebrospinal fluid (CSF) acts as a cushion for the brain. In humans, the normal pressure of CSF in the recumbent position by lumbar puncture varies from 25 to 70 mm water in infants and from 65 to 195 mm water in adults. An increase in intracranial pressure can cause characteristic symptoms of hydrocephalus, though they also may occur with normal pressure.[1] CSF flows in oscillatory motion resulting from cardiac pulsations. Cardiac systole transmits pressure wave to intracranial arteries and capillaries causing caudal flow of CSF (CSF systole) through the ventricular system, basal cisterns, and foramen magnum into the cervical subarachnoid space. Following cardiac diastole, there is reversal of flow with cephalad movement of CSF.[2] CSF flow may be altered in many intracranial and intraspinal pathologies. Changes have been seen in CSF hydrodynamics with meningitis, hydrocephalus, and cerebral edema.[3] In normal pressure hydrocephalus (NPH), aqueduct stenosis, or Chiari malformation certain CSF flow parameters can deviate strongly from normal values.[4] The abnormal values not only help in diagnosing these conditions but also act as a guide to treatment. Accordingly, Bradley et al set increased aqueductal systolic stroke volume (SV) >42 µL/cycle as a threshold value for NPH patients who benefited from surgery,[5] but we found that many of our elderly subjects not having NPH had CSF SV in the range of 40–45 µL/cycle. Hence, a need was felt to study normal CSF SV in our population. For this purpose, five parameters were defined. Peak systolic velocity is the maximum CSF velocity through the cerebral aqueduct during cardiac systole, and this CSF flow is directed caudally (during cardiac systole, blood flow is directed cranially and CSF is directed caudally to maintain total intracranial fluid volume); peak diastolic velocity (PDV) is the maximum CSF velocity through the cerebral aqueduct during cardiac diastole and this CSF flow is directed cranially; systolic flow (SF) is the total volume of CSF flowing through aqueduct over cardiac systole; diastolic flow (DF) is the total volume of CSF flowing through aqueduct over cardiac diastole; and stoke volume is the average of systolic and diastolic flow. We conducted this study to generate normative CSF flow parameters' data in the local population over 40 years of age.

## Material and Methods

The study was conducted on 100 subjects over 40 years of age. The patients who underwent magnetic resonance imaging (MRI) for some other complaint like headache and had normal MRI were included in the study. The patients where alterations in CSF hydrodynamics were suspected clinically like NPH, idiopathic intracranial hypertension (IIH), and Chiari malformations were excluded. MRI was done on 3.0T MRI system of GE make (Discovery 750w with GEM suit, Milwaukee, WI, United States) using a dedicated head coil with 32 channels. In addition to routine T1W, T2W, T2W/FLAIR, DW, SWI sequences, phase-contrast quantitative flow sequence (FOV = 22 cm, slice thickness = 4 mm, slice spacing = 1 mm, TR = 7.9 ms, TE = 3.7 ms, matrix = 256 × 256, bandwidth = 25 Hz, NEX = 2.0) was done perpendicular to the cerebral aqueduct with prospective cardiac gating using ECG leads. Thirty cardiac cycles' data were obtained. The velocity encoding was kept at 10 cm/s. The region of interest (ROI) was kept at the cerebral aqueduct in cross-section such that it covered the entire aqueduct and no extra tissue was included in it (►**Fig. 1**) The inbuilt software

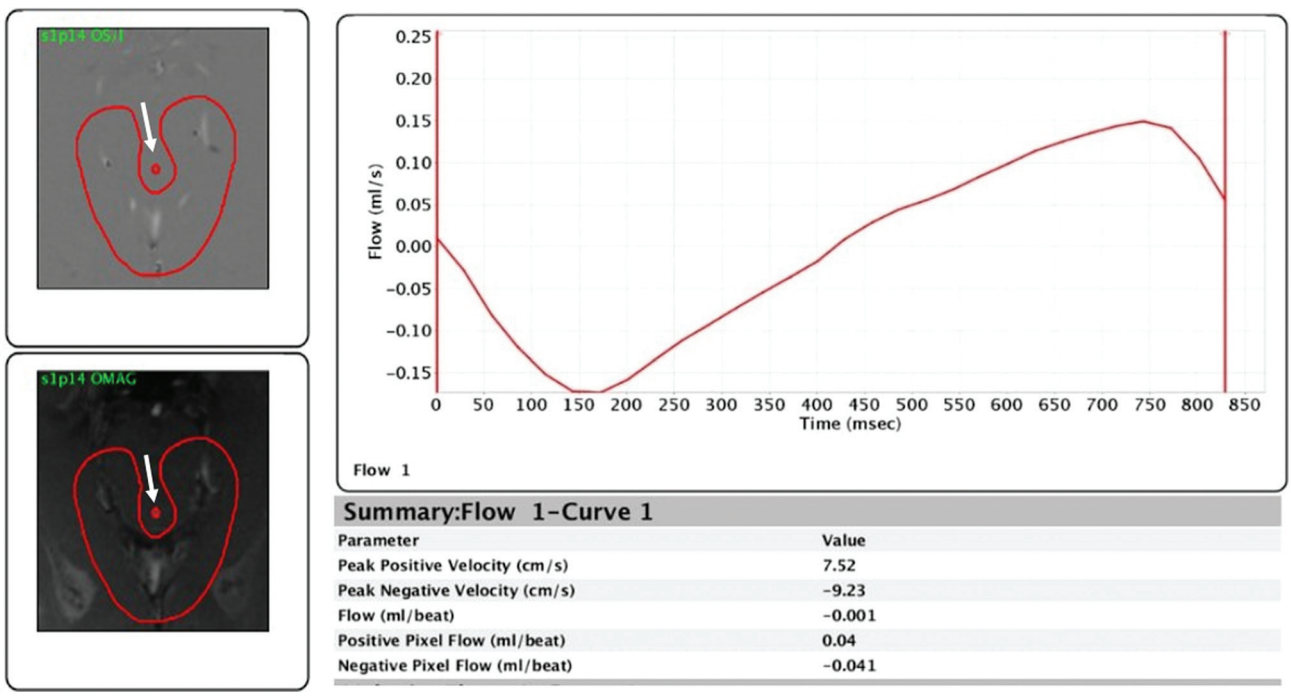


**Fig. 1** Image showing ROI on cerebral aqueduct (*arrow*), CSF flow-time graph and summary of CSF flow parameters (peak positive/diastolic velocity, peak negative/systolic velocity, flow, positive/diastolic pixel flow and negative/systolic pixel flow).

 

calculated flow-time and velocity-time graphs and calculated PSV, PDV, SF, and DF, while SV was calculated by taking average of systolic and DFs. Mean (with standard deviation) and median (with interquartile range) were calculated for continuous data. None of the five variables studied was normally distributed. Hence nonparametric tests were applied. The Spearman correlation test was used to explore the correlation between two variables. Kruskal–Wallis test was used to make group comparisons. Spearman rho, Kendall's tau, and Point-Biserial correlation coefficients were used to establish the strength of correlation between variables. $p$-Value $< 0.05$ was considered significant.

## Result

Our study population ranged from 40 to 78 years of age with mean age being $53.72 \pm 10.53$ years. There were 41 males and 59 females. PSV ranged from 1.2 to 10.5 cm/s with median (interquartile range, [IQR]) of 7.56 (5.66–9.21) cm/s, PDV ranged from 1.6 to 10.9 cm/s with median (IQR) of 5.44 (3.78–7.52) cm/s, SF ranged from 4.0 to 98.0 µL/cycle with median (IQR) of 34.00 (22.75–43.25) µL/cycle, DF ranged from 3.0 to 196.0 µL/cycle with median (IQR) of 30.00 (18.75–45.75) µL/cycle, and SV ranged from 3.5 to 142 µl/cycle with median (IQR) of 33 (20.38–44.12) µL/cycle. All the five parameters, that is, PSV, PDV, SF, DF, and SV varied significantly with age with $p$-values of 0.001 (sex-adjusted $p$-value 0.001), 0.004 (sex-adjusted $p$-value of 0.008), 0.009 (sex-adjusted $p$-value of 0.006), $<0.001$ (sex-adjusted $p$-value of $<0.001$), and $<0.001$ (sex-adjusted $p$-value of 0.001), respectively.

There was a moderate positive linear correlation between PSV and age, with the strength of association (Kendall's Tau) being 0.26 (small effect size). For every 1 year increase in age, the PSV increased by 0.07 cm/s. There was a weak positive linear correlation between PDV and age, with the strength of association (Kendall's Tau) being 0.23 (small effect size). For every 1 year increase in age, the PDV increased by 0.07 cm/s. There was a weak positive linear correlation between SF and age, with the strength of association (Kendall's Tau) being 0.24 (small effect size). For every 1 year increase in age, the SF increased by 0.48 µL/cycle. There was a moderate positive linear correlation between DF and age, the strength of association (Kendall's Tau) being 0.32 (medium effect size). For every 1 year increase in age, the DF increased by 1.05 µL/cycle. There was a moderate positive linear correlation between SV and age, with strength of association (Kendall's Tau) being 0.29 (medium effect size). For every 1 year increase in age, the SV increased by 0.77 µL/cycle. There was a significant difference between males and females in terms of PDV ($W = 1510.000$, $p = 0.035$), with the median PDV being higher in males and strength of association (point-biserial correlation) being 0.24 (medium effect size). Median PDV (IQR) was 6.25 (4.37–10) cm/s in males and 5.07 (3.51–6.56) cm/s in females. There was a significant difference between males and females in terms of DF ($W = 1495.500$, $p = 0.045$), with the median DF being higher in males and strength of association (point-biserial correlation) being 0.22 (small effect size). Median DF (IQR) was 33 (25–67) µL/cycle in males and 28 (15.5–40.5) µL/cycle in females. However, when adjusted for age, only PDV showed significant variation with sex ($p = 0.038$), being higher in males.

As the parameters showed an increasing trend with age and the increase per year was too small, the patient population was grouped according to decades, and decadal changes in values were also evaluated. When decadal means and medians were correlated with age using the Kruskal–Wallis test, all five parameters again showed significant variation with age. ►**Table 1** shows the decadal range and medians (IQR) for PSV, PDV, SF, DF, and SV along with corresponding $p$-values showing the association of age with these parameters. This table clearly shows that PSV, PDV, SF, DF, and SV increased slowly but definitely with age. The difference was discernible in each parameter when decadal median values were considered as seen in the table. All the parameters except SF peaked in seventh decade (61–70 years). As the range suggests, there is a wide variation in values of normal CSF parameters for each decade. ►**Fig. 2** shows the association of PSV, PDV, SF, DF, and SV, respectively, with age by means of scatter plots.

Only two parameters, PDV and DF varied significantly with sex with $p$-values of 0.035 and 0.045, respectively. When adjusted for age, only PDV showed significant variation with sex ($p = 0.038$). The rest of the parameters did not show significant variation ($p$ values $<0.05$) with sex. ►**Table 2** shows medians (IQR) for PSV, PDV, SF, DF, and SV for males and females along with corresponding $p$-values (Wilcoxon Mann–Whitney U test used for comparison). Both PDV and DF were higher in males as compared to females.

## Discussion

Our results show that age has a significant bearing on CSF flow parameters. Various parameters show a slow but definitive increase with age. Decade-wise median values clearly show this. All the values except SF peaked in seventh decade (61–70 years). Only PDV showed a significant correlation with sex when adjusted for age. Sartoretti et al also postulated that between 6 and 18% of the variability in all parameters may be explained only by two factors, age and sex.[6] They studied 10 CSF flow parameters with respect to age and sex and found that SV, forward flow volume, backward flow volume, as well as peak velocity were significantly influenced by both age and sex. In our study also, PSV, PDV, SF, DF, as well as SV were significantly affected by age, but only PDV significantly correlated with sex. Other parameters did not correlate significantly with sex. This difference may be because Sartoretti et al included all age groups (17 to 88 years), while we included subjects above 40 years of age. Many females in this age group were postmenopausal. Estrogen and progesterone can influence both neural and hormonal systems that regulate the volume and osmolality of body fluids. Hormone concentrations change after menopause in women, thus impacting an individual's ability to regulate body fluids. The CSF secretion is a two-stage process.[7] The osmotic pressure gradient between fenestrated

 

**Table 1** Table showing decadal median (IQR) and range of various CSF flow parameters along with *p*-value of their association with age

| Parameter | | Age (Years) | | | | *p*-Value |
|---|---|---|---|---|---|---|
| | | 40–50 ($n = 47$) | 51–60 ($n = 27$) | 61–70 ($n = 16$) | 71–80 ($n = 10$) | |
| Peak systolic velocity (cm/s) | Median (interquartile range) | 6.36 (4.86–7.94) | 8.31 (5.31–9.36) | 9.02 (7.97–9.31) | 8.1 (7.7–9.17) | 0.004 |
| | Range | 1.93–9.88 | 1.24–9.68 | 5.9–10.5 | 6.16–9.68 | |
| Peak diastolic velocity (cm/s) | Median (interquartile range) | 4.6 (3.44–6.22) | 5.51 (3.51–7.37) | 8.05 (5.84–10.2) | 6.36 (4.7–9.44) | 0.007 |
| | Range | 1.57–10.4 | 1.56–10.6 | 3.38–10.9 | 2.68–10.3 | |
| Systolic flow (µL/beat) | Median (interquartile range) | 26 (19–41.5) | 34 (22–43) | 37 (30.75–50.25) | 38.5 (36.25–60.5) | 0.012 |
| | Range | 4–98 | 7–52 | 26–82 | 26–89 | |
| Diastolic flow (µL/beat) | Median (interquartile range) | 25 (14–38) | 30 (19–43) | 54.5 (39–70.25) | 32 (29.25–73.25) | <0.001 |
| | Range | 3–128 | 8–85 | 20–129 | 27–196 | |
| Stroke volume (µL/beat) | Median (interquartile range) | 25 (16.25–39.75) | 33 (20.75–43) | 45.25 (34.5–66.12) | 35.5 (33.12–66.88) | 0.001 |
| | Range | 3.5–113 | 8–65.5 | 24–80 | 26.5–142 | |

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range.

capillary endothelium and choroidal interstitial space leads to passive filtration of plasma followed by active transport of ultrafiltrate across the choroidal epithelium into the ventricular spaces. As age increases, the compliance of capillaries decreases and capillary pressure increases, while brain atrophy may lead to the expansion of interstitial fluid and a decrease in its pressure leading to a net increase in pressure gradient between capillary endothelium and interstitial space, the driving force behind CSF production. Hence, there may be an increase in CSF production and SV with age.

There is great variability in various parameters across the literature. Various studies have not calculated the parameters in a uniform way making it difficult to make comparisons. This may also be attributed to physiological state, ethnicity, technique, and machine. The stroke volume upper limit is now suggested to be variable between institutions due to intrinsic scanner differences. Some differences may also arise due to technique. There is variability in values of parameters at the upper and lower parts of the cerebral aqueduct[8] and also on compressing internal jugular veins.[9] Hence, normative data should be measured for each make of scanner.

Most of the normal subjects have been studied as controls for comparison with some pathological cases. A large number of normal subjects ($n = 47$) have been studied by Luetmer et al as part of a larger study, but they have not generated separate CSF flow parameters' data for these subjects.[10] Neither is it clear what was the age range of their normal subjects, making it really difficult to use it as a reference for normal data. Sharma et al have given the value of only peak flow velocity in 13 subjects with an average age of 64.9 years[11] and Lakhera et al have given peak velocity and SV in 20 normal subjects[1] but have not elaborated the age range or average age of these normal subjects. Hence, these studies are difficult to use as a baseline as they have a very small sample size and have studied very few parameters. Our study with a sample size of 100, studying five CSF flow parameters (PSV, PDV, SF, DF, and SV), assessing their correlation with age and sex and providing decadal means in terms of these five parameters can very well act as normative data for GE scanner for local population. Another such study comparable in sample size and parameters is that by Sartoretti et al,[6] but they studied a wider age range (17–88 years). Theirs was a European study and may not be appropriate for the Indian population due to difference in ethnicity. Hence, we conducted this study to generate normative data for the Indian population.

Normal data are very useful. It helps in distinguishing NPH form atrophy.[12] Lakhera et al used CSF flow dynamics to distinguish viral from nonviral meningitis which was quite helpful in cases where contrast could not be administered.[1] CSF is a multifunctional entity, not only in diagnosing central nervous system disorders but also in further clinical monitoring and prognosis after treatment.[13] Hussein et al evaluated the prognostic value of MRI-CSF flowmetry for shunt responsiveness in patients with idiopathic normal pressure hydrocephalus (iNPH) and its usefulness as a predictor of post-CSF diversion favorable outcome.[14] To make full use of

 

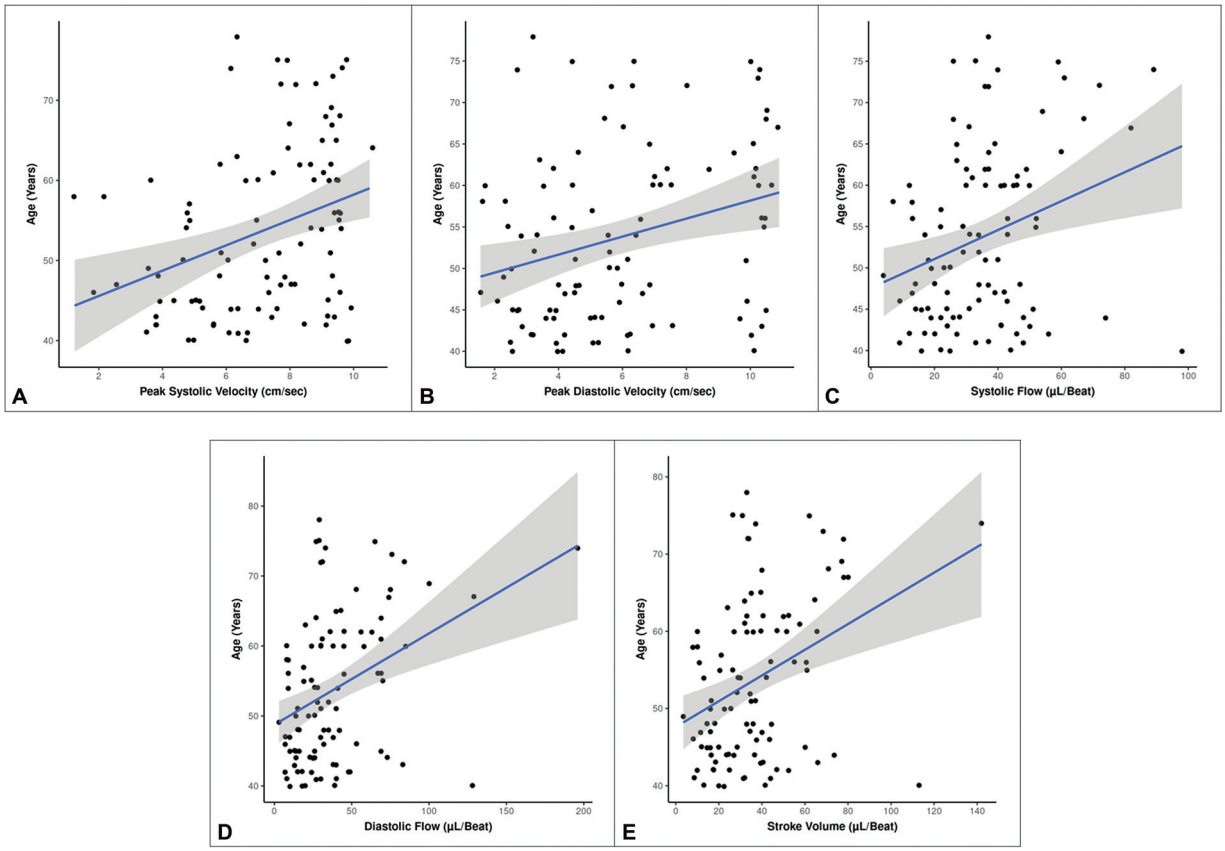


**Fig. 2** (**A**) Scatter plot showing association between age and peak systolic velocity. (**B**) Scatter plot showing association between age and peak diastolic velocity. (**C**) Scatter plot showing association between age and systolic flow. (**D**) Scatter plot showing association between age and diastolic flow. (**E**) Scatter plot showing association between age and stroke volume.

**Table 2** Table showing median (IQR) and range of various CSF parameters in males and females along with *p*-value of their association with sex (only parameters showing significant association with sex are shown in the table)

| Parameter | | Sex | | |
|---|---|---|---|---|
| | | Males ($n = 41$) | Females ($n = 59$) | *p*-Value |
| Peak systolic velocity (cm/s) | Median (interquartile range) | 8.29 (6.31–9.27) | 7.33 (4.92–8.8) | 0.093 |
| | Range | 1.24–9.88 | 1.93–10.5 | |
| Peak diastolic velocity (cm/s) | Median (interquartile range) | 6.25 (4.37–10) | 5.07 (3.51–6.56) | 0.035 |
| | Range | 1.56–10.6 | 1.57–10.9 | |
| Systolic flow (µL/cycle) | Median (interquartile range) | 36 (29–48) | 31 (22–41.5) | 0.060 |
| | | 4–98 | 9–82 | |
| Diastolic flow (µL/cycle) | Median (interquartile range) | 33 (25–67) | 28 (15.5–40.5) | 0.045 |
| | Range | 3–196 | 7–129 | |
| Stroke volume (µL/cycle) | Median (interquartile range) | 35 (27–55) | 32 (18.25–41) | 0.082 |
| | Range | 3.5–142 | 8–80 | |

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range.

the diagnostic and prognostic potential of CSF flow parameters, it is essential to have normative data. Our study is a step in this direction.

The most important of CSF flow parameters is SV which is defined as the mean volume of CSF passing through the aqueduct in craniocaudal and caudocranial direction. Bradley concluded that increased CSF SV is more important predictor of shunt response than the high CSF flow void sign in NPH.[15] Tawfik et al assessed PSV, peak mean velocity, and aqueductal CSF SV concluding that SV had better agreement and repeatability and was more accurate than peak mean velocity for the diagnosis of NPH.[16] Bradley et al stated

 

that patients who responded well to CSF diversion surgeries for iNPH had at least twice the aqueductal SV of healthy elderly patients, with increased aqueductal systolic SV > 42 µL/cycle set as a threshold value for patients who benefited from surgery.[5] This threshold of 42 µL does not always hold good. In our study itself, median SV was 45.25 µL/cycle in 61 to 70 age group. Hence, the best is to have own normative data, with two times normal value indicative of shunt responsiveness in conjunction with response to CSF drainage.

Our study has few limitations too. Though the sample size is reasonable, it may still have limited impact especially when the aim of the study is to generate normative data. Second, our subjects had normal MRI but were not totally asymptomatic. They had some other indications for MRI like headache. Hence, subtle abnormality not evident on MRI may confound the data. It was not possible to scan normal subjects due to ethical considerations. The data are also scanner dependent. Hence, our data can act as baseline for normal CSF flow parameters for at least 3.0T GE make scanners in the local population.

## Conclusion

All five CSF flow parameters studied (PSV, PDV, SF, DF, and SV) vary positively with age and this variation is linear. The normal decadal median values calculated for CSF flow parameters may be beneficial instead of using the single value that is common for all age groups (as the parameters are linearly increasing with age) and help in defining conditions like NPH. Only PDV showed significant association with sex when adjusted for age.

Ethical Approval
The study was approved by the institutional ethics committee and was in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Funding
None.

Conflict of Interest
None declared.

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