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Defining the Normal Range of Cerebrospinal Fluid Opening Pressure in Adults: A Systematic Review

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Defining the Normal Range of Cerebrospinal Fluid Opening Pressure in Adults: A Systematic Review

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Defining the Normal Range of Cerebrospinal Fluid Opening Pressure in Adults: A Systematic Review

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It has been theorized that the visual changes observed in the astronaut population described by the Spaceflight Associated Neuro-ocular Syndrome (SANS) are related to elevated intracranial pressure (ICP). To better understand the mechanism of SANS and provide adequate prevention, treatment, and countermeasures for this population, direct measurement of ICP via lumbar puncture has been suggested. However, the normal range of cerebrospinal fluid opening pressure (CSFOP) is first needed to interpret values obtained via lumbar puncture in the astronaut population. Many clinical guidelines utilize an upper limit of normal CSFOP of 20 cmH2O, but clinical and research experience suggests many normal individuals may have CSFOP above this cutoff. The aim of this study was to provide a description of the normal CSFOP range in adults via a qualitative systematic review of the literature. The PubMed (MEDLINE) database was searched including records published through June of 2018. Reference lists from eligible articles were manually reviewed and physicians in relevant fields contacted to ensure a comprehensive search. The primary outcome was the mean CSFOP with standard deviation where reported. An additional 9 items were abstracted by a single reviewer including range of

CSFOP. Overall, 164 records were identified for screening, with 12 studies remaining after inclusion and exclusion criteria were applied. Data were abstracted by the author and presented in table format. Mean CSFOP ranged from 12.98 to 18.8 cmH2O where reported. Of the 12 studies included, six (50%) reported subjects with a CSFOP that exceeded 20 cmH2O. Five (42%) studies recruited healthy volunteer subjects only, and six (50%) included subjects undergoing diagnostic LP who did not have a diagnosis that is thought to affect ICP. Studies involving only healthy volunteers generally had a smaller sample size, limiting information available on the range of CSFOP in healthy, asymptomatic individuals. Future work will involve a quantitative meta-analysis of identified records in order to provide a clear definition of CSFOP for comparison to the astronaut population.

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List of Abbreviations

CI	Confidence Interval
CSF	Cerebrospinal Fluid
CSFOP	Cerebrospinal Fluid Opening Pressure
CNS	Central Nervous System
HA	Headache
ICP	Intracranial pressure
JSC	Johnson Space Center
LP	Lumbar puncture
NASA	National Aeronautics and Space Administration
OP	Opening pressure
PO	Per os (by mouth)
SANS	Spaceflight Associated Neuro-ocular Syndrome
SD	Standard Deviation
UTMB	University of Texas Medical Branch

Chapter 1 Introduction

RESEARCH QUESTION

Astronauts have been observed to experience changes in visual acuity (hyperopia), globe flattening, optic disc edema, and choroidal folds following spaceflight. This collection of visual signs and symptoms is known as the Spaceflight Associated Neuro-ocular Syndrome (SANS) [1] [2]. One of the proposed mechanisms for SANS is elevated intracranial pressure (ICP). Direct measurement of ICP via cerebrospinal fluid (CSF) opening pressure has only been performed in a handful of subjects without pre-flight values available for comparison. To protect the health and performance of the astronaut population, an occupational surveillance program measuring CSF opening pressures via lumbar puncture has been proposed. Such a program would potentially involve performing lumbar punctures pre-flight, during flight, and post-flight. However, the normal range for CSF opening pressure in adults is not clearly defined in the literature and differs from clinical cutoffs. Studies indicate that between 16 and 40% of normal individuals may have CSF opening pressures greater than the previously accepted clinical upper limit [3] [4] [5]. A clear description of normal CSF opening pressure in adults is needed to provide a baseline for comparison and allow for diagnostic accuracy. The aim of this study is to perform a qualitative systematic review of the literature to describe the normal range of lumbar puncture CSF opening pressure in adults.

OBJECTIVES

The primary objective of this review is to evaluate the range of CSF opening pressure (CSFOP) as obtained by lumbar puncture in normal adult subjects. Subjects may include both asymptomatic and symptomatic patients undergoing experimental or diagnostic lumbar puncture in a clinic or hospital setting. Subjects should not have any diagnosis that would alter intracranial pressure. A qualitative systematic review will be performed to summarize findings from primary literature characterizing the range of CSFOP obtained via lumbar puncture in adults.

RATIONALE FOR THE REVIEW

The normal range of CSF opening pressure as obtained by lumbar puncture (LP) is not clearly defined in the literature for healthy, asymptomatic individuals. Clinical cutoffs for normal CSF opening pressure have relied on recommendations in historical neurology and neurosurgery textbooks. The upper limit of normal used clinically has historically been 20 cm of H2O [5] [6]. However, anecdotal clinical experience as well as a number of research studies have suggested that there is a significant portion of normal subjects who fall outside of the historically reported normal range [5] [6]. The lack of a well-defined normal range makes it difficult to compare populations and provide clear diagnostic and research criteria for elevated intracranial pressure (ICP). It has been proposed that elevated ICP is responsible for visual system changes experienced by the astronaut population. Therefore, a normal range for CSF opening pressures is needed for research interpretation and to develop an occupational surveillance program for astronaut crewmembers suspected to be at risk of elevated intracranial pressure.

Chapter 2 Background

SIGNIFICANCE

It has been proposed that elevated ICP may be occurring in spaceflight and could potentially be a contributor to visual disturbances encountered in human spaceflight experience. Astronauts have been found to have changes in visual acuity (hyperopia), globe flattening, optic disc edema, and choroidal folds after exposure to spaceflight. This collection of symptoms and findings is known as the Spaceflight Associated Neuro-ocular Syndrome (SANS) [1] [2]. Very few lumbar punctures or other direct means of measuring ICP have been performed in the astronaut population. Lumbar punctures that have been performed were typically done post-flight in individuals with clinical findings. The baseline intracranial pressure and changes experienced during and after spaceflight are therefore unknown. In order to better protect human health and performance for the astronaut population, an occupational surveillance program for monitoring ICP has been proposed utilizing lumbar puncture CSF opening pressure. Lumbar puncture is a commonly performed, minimally invasive procedure in which the CSF opening pressure can be obtained by inserting a small needle into the back. CSF opening pressure is an adequate estimation of ICP, and LP carries a low risk to the astronaut crew. However, a particular hurdle to developing such a program includes clearly defining normal values for CSF opening pressure, as the literature is limited on this front. Additionally, research studies being performed to further characterize the ICP levels of astronauts pre and post-flight would benefit from clearly identifying a normal range for CSF opening pressure in a normal adult population. The aim of this project is to perform a systematic review of the literature to describe the normal range of CSF opening pressure in adults.

EXISTING KNOWLEDGE AND GAPS

The normal range of CSF opening pressure has historically been reported in textbooks with an upper limit between 15 cm H20 and 20 cm H20 [6]. However, clinicians anecdotally noticed that a CSF opening pressure greater than 20 cm H2O in normal individuals was not uncommon. Studies in the 1970s and 1980s raised the question as to whether the accepted normal range was accurate, as they found that 16 to 25% of normal subjects had CSF opening pressures above the previously reported upper limits of normal [3] [4] [6]. A more recent study by Bo et al in 2010 revealed that approximately 40% of normal patients had CSF opening pressures greater than 20 cm H20 [5]. A qualitative review article by Lee et al in 2014 presented findings in recent literature including both adult and pediatric normal CSF opening pressure ranges. The findings of this review article support a broader range of 6 to 25 cm H2O as normal CSF opening pressure [6]. The largest study included in the review by Lee et al was a study performed by Fleischman et al in 2012 which involved a retrospective chart review of 12,118 patients after inclusion and exclusion criteria were met. These patients were 20 years and older and underwent diagnostic LPs at the Mayo Clinic. While this is the largest known study to report on normal range of CSF opening pressure, this was not the purpose of the study. The study sought to evaluate the impact of age, sex, race, and BMI on CSF opening pressure and also to correlate this with intraocular pressure. As such, they excluded any patients with CSF opening pressure below 6 or above 25 cm H2O. While this remains the largest source of data on normal CSF opening pressure, it is somewhat limited as the data were censored both on the lower and upper ends [7]. There is concern that if a greater number of subjects had CSFOP greater than 20 cmH2O, censoring may result in a falsely low mean value. One of the major limitations of available literature is that subjects that were included underwent diagnostic lumbar puncture. This could have been for workup of headache, vision changes, altered mental status, meningitis rule out, etc. Studies that included subjects undergoing diagnostic LPs typically excluded individuals who were found to have conditions that would affect ICP levels. While this is an imperfect approach to defining a normal population, researchers were often limited by time, resources, and ethical considerations as an LP is a minimally invasive procedure that may cause discomfort, pain and a small risk to the patient [5] [8]. The only studies that report a normal CSF opening pressure range for young, healthy volunteers are of very low sample size ranging from 8 to 105 participants [9] [10] [3] [11] [12].

While the review article by Lee et al in 2014 is helpful in supporting a definition of normal CSF opening pressure with a higher upper limit, it reports data on only 4 studies with one study including primarily pediatric patients [6]. As such, a comprehensive review of the literature is needed to better define the normal range of CSF opening pressure in order to provide a baseline for comparison for researchers and the development of an occupational surveillance program for astronauts at potential risk for elevated ICP.

Chapter 3 Methods

SEARCH STRATEGY

A qualitative systematic review of the literature was performed using the PubMed (MEDLINE) database. Although the majority of studies of interest were observational and did not involve an intervention, the Cochrane guidelines were utilized in the development of protocols and conducting the systematic review [13]. Syntax for the PubMed database search criteria is provided in Figure 1. The last comprehensive search of the PubMed database was performed in June of 2018. There was no limitation placed on publication date in the search criteria. Titles and abstracts of identified records were then screened for relevance and full-text articles assessed for inclusion and exclusion criteria. The reference list from full-text articles identified through final screening were manually reviewed for relevant literature on the normal range of CSF opening pressure. Any records identified in this manner were then included in the screening process. Manual review of references lists was performed to ensure a comprehensive review of relevant literature.

Search Syntax: (normal OR reference OR observational) AND (lumbar puncture) AND (cerebrospinal OR CSF) AND (opening pressure)

Figure 1: Search Syntax Utilized for PubMed (MEDLINE) Database

Furthermore, physicians in relevant fields including neurology critical care and aerospace medicine were contacted for relevant literature. The UTMB Galveston library staff also provided additional suggestions for relevant literature.

INCLUSION AND EXCLUSION CRITERIA

After any duplicate records were removed, records were screened based upon title and abstract for inclusion and exclusion criteria as well as relevance. Full-text articles were then assessed for eligibility. Studies were included that reported CSF opening pressure data obtained via lumbar puncture for individuals age 18 and above. Pediatric data were excluded from this study as the population of interest for comparison is the astronaut population. Non-human data and non-English language records were excluded. Case reports, review articles, and textbook chapters which did not contain primary data on CSF opening pressure were excluded. Case reports were specifically excluded given the small subject size and presence of pathology or diagnoses that may affect ICP.

Studies involving healthy volunteer subjects as well as those undergoing diagnostic lumbar punctures were included. Limiting inclusion to only studies with healthy, asymptomatic subjects would be too limiting as they are rare and of very small sample size [3] [10] [11]. However, subjects were excluded if found to have medical conditions that impacted intracranial pressure. Studies were also excluded if there was insufficient information as to whether individuals with diagnoses affecting ICP were included in the results. The lumbar puncture may have been performed in the hospital or outpatient clinic setting. Studies were excluded if an intervention or medication thought to impact intracranial pressure was present. A list of inclusion and exclusion criteria is provided in Table 1.

Inclusion Criteria:	**Exclusion Criteria:**
English language records	Non-English language records
Primary CSFOP data	Case report or review article
CSFOP obtained via LP	Secondary referencing of CSFOP (not primary source)
Diagnostic or experimental LP	Insufficient data (lacking CSFOP or diagnoses)
Human subjects	Non-human subjects
Adult subjects (Age $\geq$ 18 yrs)	Pediatric subjects (Age < 18 yrs)
	Subject diagnoses that would affect ICP
	Medications, interventions, or surgeries that would affect ICP

Table 1: Study Inclusion and Exclusion Criteria

DATA EXTRACTION

For remaining eligible studies, data were abstracted by the author and presented in table format. The primary outcome of interest was lumbar puncture opening pressure measured in centimeters of water (cm H2O). Values reported in different units were converted to centimeters of water (cm H2O) for consistency. Other variables collected included age, gender, and BMI of the subjects. Additionally, needle size, type of manometer, patient positioning, and presence or absence of local anesthesia were abstracted where available. For studies which presented CSF opening pressure data means and standard deviation (SD) for subgroups, the overall mean and SD were calculated using the formula for combining groups provided in the Cochrane Handbook for Systematic Reviews of Interventions Table 7.7a [13]. These formulas are provided for reference in Figure 2 below. These calculations allowed for consistent reporting of values across studies.

Sample Size: $$N_{tot} = N_1 + N_2$$

Mean: $$M_{tot} = \frac{N_1M_1+N_2M_2}{N_1+N_2}$$

SD: $$SD_{tot} = \sqrt{\frac{(N_1-1)SD_1^2+(N_2-1)SD_2^2+\frac{N_1N_2}{N_1+N_2}\left(M_1^2+M_2^2\right)-2M_1M_2)}{N_1+N_2-1}}$$

Figure 2: Equations for Combining Groups Adapted from the Cochrane Handbook for Systematic Reviews of Interventions [13]

QUALITY ASSESSMENT

The majority of studies included in this systematic review were observational and did not involve an intervention. Study types varied and included descriptive analysis, observational cohort, and cross-sectional studies. Given this, a modified format of the NIH

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was utilized as an assessment of quality for studies included in the full-text review [14]. Quality assessment was performed after data extraction to limit any bias in reporting.

Chapter 4 Results

SEARCH RESULTS

PubMed search using the syntax listed in Figure 1 above identified 144 records. An additional 23 records were identified via other sources including manual review of the reference listings of eligible full-text records and expert contribution. After duplicate records were removed, a total of 164 records were screened based on title and abstract. One-hundred twenty-five of these records were excluded for study type, presence of diagnoses in the subjects which may have altered ICP, pediatric studies, animal studies, and non-English language. Thirty-nine full-text articles were assessed for eligibility and 27 were excluded for reasons detailed in Figure 3. The remaining 12 studies were included in a qualitative synthesis of information in table format after data abstraction.

SELECTION PROCESS

A flow diagram of the systematic review process utilized is provided in Figure 3 according to PRISMA guidelines [15].

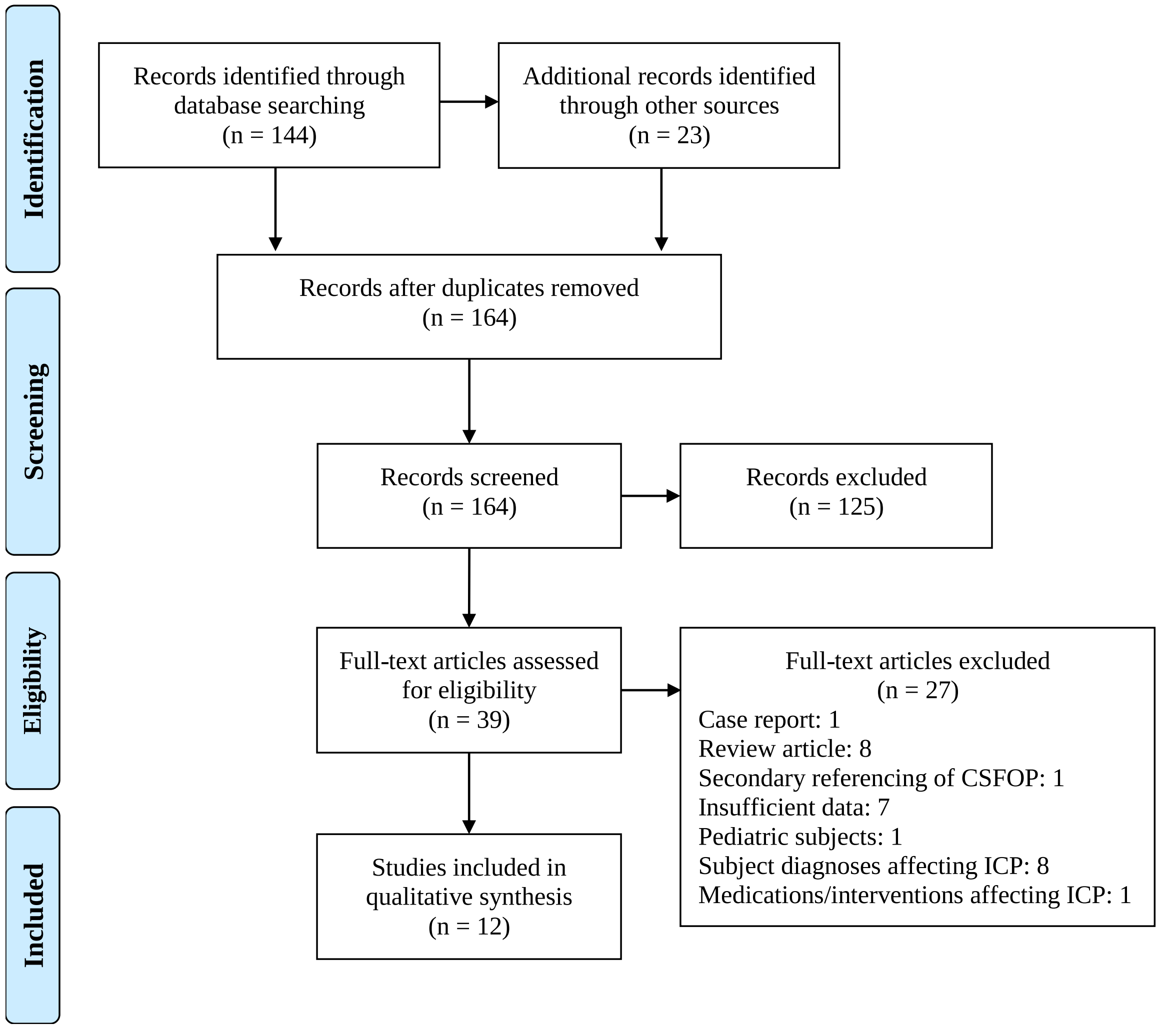

Figure 3: Flow Diagram of Study Selection using PRISMA Guidelines [15]

DESCRIPTION OF STUDIES

Publication Dates

Studies identified range from publication in 1933 to 2012. One reason for manually reviewing reference listings of eligible full-text papers from the PubMed database search was to capture older publications which may not otherwise be available online. One of the final records included in the qualitative synthesis by Tourtellotte et al was in book format obtained from the University of Michigan Library. Online versions of the remaining records were available, and these records were in manuscript format.

Sample Sizes

Sample sizes of included studies ranged from 8 to 12,118. No limitation was placed on sample size for inclusion as the smaller sample studies tended to include healthy volunteers. The studies with larger sample sizes included subjects who were undergoing diagnostic lumbar puncture but were not diagnosed with a condition thought to impact ICP. Although these studies were better powered, the subjects were not strictly normal, healthy volunteers. The largest study with healthy subjects identified had 105 participants. Six of 12 studies identified included subjects undergoing diagnostic LPs; five studies performed LPs on healthy volunteers; and one study included patients undergoing spinal anesthesia for unrelated urologic, orthopedic, or gynecologic reasons.

Subject Demographics

The mean age of subjects from the identified studies varied from 23 to 54.4 years in the Fleischman et al study. This study broke down groups into subgroups by age. Certain subgroups contained in this paper may be more applicable to the astronaut population as the total cohort had a maximum age of 95 years of age. Gender distribution was identified in all studies but one. Overall men made up 49% and women 51% of subjects, where listed. Quantitative data on BMI was available in 4 of 12 studies included. Qualitative information on BMI was provided in an additional 2 studies. The remaining 6 studies did report BMI for applicable subjects.

Lumbar Puncture Procedure and Equipment

Needle size was consistently reported in all but one study, and 4 of the 12 studies utilized more than one needle size. Local anesthesia was used in 6 of the studies and 3 studies explicitly stated that local anesthesia was not provided. The remaining 3 studies did not clearly identify whether or not local anesthesia was utilized. All of the 12 studies identified explicitly stated that patient positioning was in the lateral decubitus or lateral recumbent position. Hip and knee positioning were less commonly mentioned and there was a mix of open end manometers and isovolumetric measuring devices utilized. The majority of studies were prospective and observational. There were two retrospective chart reviews included which also had the largest sample sizes. Study setting included both hospital and outpatient clinics.

CSF Opening Pressure

The largest study included by Fleischman et al included 12,118 patients undergoing diagnostic LPs at the Mayo Clinic in Rochester, MN [7]. The study includes the largest sample size identified for a patient population which excluded any diagnoses that would alter ICP. However, the aim of the study was not to identify a normal range but instead to examine the effect of age, sex, race, and BMI on CSFOP. Given this, the authors chose to exclude patients with a CSFOP less than 6 cmH2O or greater than 25 cmH2O. While reasonable for the aims of the study, this does censor the data with respect to identifying the normal range of CSFOP for the purposes of this systematic review. 8.4% of patients fell outside of the 6 to 25 cmH2O CSFOP range in this study [7]. Of note, data is presented in subgroups by age. For consistency, mean CSFOP and SD were combined for all subgroups in Table 2. However, it may be valuable to use relevant age subgroups when looking at the astronaut population, although this would decrease the sample size. For instance, in subjects age 20 to 49 years the mean CSFP was 15.63 cmH2O (SD 3.67 cmH2O), higher than the mean CSFOP for all subgroups combined. This article did find that CSFOP decreases with age, thus comparison with similarly aged subgroups may be beneficial for the population of interest.

Bø et al examined patients in different clinical settings with acute, chronic, or no pain to observe differences in CSFOP associated with age or sex. As the secondary headache and outpatient neurology clinic subgroups had potential for diagnoses affecting ICP, these were excluded from this systematic review. The primary headache subgroup had a mean CSFOP of 19.3 cmH2O (SD 6.1 cmH2O), and the myelography subgroup had a mean CSFOP of 17.3 cmH2O (SD 4.2 cmH2O). These subgroups were combined for the mean CSFOP of 18.8 cmH2O (SD 5.7 cmH2O) reported in Table 2. Of note, 11 patients in the primary headache subgroup and four patients in the myelography subgroup had CSFOP in the 7 to 10 cmH2O range. Seven patients in the primary headache subgroup and one patient in the myelography subgroup actually had CSFOP above 30 cmH2O [5].

Whiteley et al sought to describe a reference range for normal CSFOP and evaluate impact of BMI. In a study of 242 patients, they identified a median CSFOP of 17 cmH2O with 95% CI of 10 to 25 cmH2O. Patients with CSFOP up to 28 cmH2O did not have symptoms of elevated ICP including headache. Examination of Fig 1 from Whiteley et al indicates that 68 patients (28.1%) had CSFOP of 20 cmH2O or greater. The authors cautioned diagnosing individuals with intracranial hypertension with CSFOP less than 25 cmH2O [8].

A study by Albeck et al in 1991 had a very small sample size of 8 subjects, but it included only healthy young volunteers. In this study, CSFOP ranged from 9.52 to 20.39 cmH2O. The calculated median CSFOP from these subjects was 15.63 cmH2O [10].

The study by Corbett et al in 1983 evaluated CSFOP in four subgroups including an acute pseudotumor cerebri, chronic pseudotumor cerebri, normal obese, and normal non-obese subgroups. There were individuals with CSFOP between 20 and 25 cmH2O in each subgroup. For the purpose of this systematic review, the pseudotumor cerebri subgroups were excluded as they had pathology that raises ICP. The normal nonobese subgroup had a mean CSFOP of 13.6 cmH2O (SD 3.76) and the normal obese subgroup had mean CSFOP of 16.7 cmH2O (SD 3.646 cmH2O). Of the normal obese subjects, 25%

had CSFOP between 20 to 25 cmH2O. 7% of the nonobese subgroup had CSFOP between 20 and 25 cmH2O [4].

The study by Gilland et al in 1974 included 31 young, healthy volunteers with two different needle sizes utilized for the procedure. The 22-g and 26-g subgroup data were combined for reporting in Table 2. The mean CSFOP for the 22-g subgroup was 14.5 cmH2O (SD 3.7 cmH2O) with a 95% CI of 4 to 25 cmH2O. The mean CSFOP for the 26-g subgroup was 15.7 cmH2O (SD 3.6 cmH2O) and a 95% CI of 5 to 26 cmH2O [3].

Five studies reported a CSFOP range below 20 cmH2O, and the study by Tourtellotte et al was lacking information on the range of CSFOP [16] [9] [17] [11] [12] [18]. Of the studies indicating that CSFOP range was below 20 cmH2O, 3 included diagnostic LPs and 2 included healthy volunteer subjects.

SUMMARY OF FINDINGS

Table 2 below contains a summary of the findings for CSFOP in the 12 studies identified in this systematic review as well as demographic and technique information where available. CSFOP was reported in a variety of units in the various papers including cmH2O, mmH2O, mmHg, cmCSF, mmCSF, and cm0.15M NaCl. For consistency of reporting, these values were converted to cmH2O after data abstraction. Values reported in mmHg were converted to cmH2O using the conversion factor 1.35951. Values reported in cmCSF or cm0.15M NaCl were assumed to be in a 1:1 ratio with cmH2O. For certain studies, information was presented in subgroups or only certain subgroups of subjects met inclusion/exclusion criteria. In these instances, combined sample sizes, means, and standard deviations were performed using the equations provided in Figure 2. The groups combined were annotated and calculated values identified. Median values for CSFOP were lacking in the majority (8/12) of the studies, and therefore means with standard deviation are included in Table 2.

Study	Sample Size	Age (Years)	Gender n (%)	BMI	LP Type	Needle Size	Local Anes.	CSFOP Mean (cmH2O)	CSFOP Range (cmH2O)	Original Units	Notes
Fleischman et al 2012	12,118	Mean: 54.4 (SD 15.2) Median: 55	M 5894 (49%) F 6224 (51%)	Mean: 26.7 (SD 5.2) Median: 26.1	Diagnostic	20-g	Yes	14.87 (SD 3.73)†	6.00-26.35	mmHg	Excluded patients with CSFOP <6 or >25 cmH2O; All age subgroups combined
Bø et al 2010	235	Mean: 45.9 (SD 16.6)†	M 95 (40%) F 140 (60%)	N/A	Diagnostic	20-g	No	18.8 (SD 5.7)†	N/A	cmH2O	Primary HA and myelography subgroups combined
Bono et al 2009	120	Mean: 38.8 (SD 13.3)	M 49 (41%) F 71 (59%)	Mean: 28.8 (SD 5.7) Range: 18-50.3	Diagnostic	22-g 20-g	Yes	13.23 (SD 3.80)	6.5-19.5	mmH2O	Only normal MRV subgroup included
Whiteley et al 2006	242	Median: 45 Range: 18-88	M 108 (45%) F 134 (55%)	Median: 26 Range: 13-52	Diagnostic	22-g 20-g	Yes	Mean: N/A Median: 17 95% CI: 10-25	9-28	cmCSF	
Edsbagge et al 2004	19	Mean: 25.4 Range: 21-35	M 19 (56%) F 15 (44%)	N/A	Healthy	22-g	No	13.6 (SD 3.1)	9.2-19.1	cmH2O	Age/gender reported for initial 34 patients recruited
Bono et al 2002	100	Mean: 39.72 (SD 14.6) Range: 15-69	M 24 (24%) F 76 (76%)	Mean: 26.0 (SD 5.4) Range: 18.3-46.5	Diagnostic	20-g	N/A	12.98 (SD 3.49)	6.0-19.2	mmH2O	
Albeck et al 1991	8	Range: 22-28	M 2 (25%) F 6 (75%)	N/A	Healthy	18-g	Yes	14.95 (SD 2.72)	9.52-20.39	mmHg	
Corbett et al 1983	56	N/A	M 42 (75%) F 14 (25%)	Obese: 41 Non-obese: 15	Spinal Anesthesia	22-g	Yes	15.87 (SD 3.90)†	N/A	mmH2O	Normal obese and non-obese subgroups combined
Gilland et al 1974	31	Mean: 23 Range: 20-27	M 22 (71%) F 9 (29%)	"Normal"	Healthy	22-g 26-g	No	15.1 (SD 3.6)†	8-24	cm0.15M NaCl	22-g and 26-g subgroups combined
Gilland 1969	15	Mean: 24.5 Range: 21-32	M 6 (40%) F 9 (60%)	N/A	Healthy	24-g	N/A	14.4 (SD 3.1)	9-20	cmH2O	
Tourtellotte et al 1964	105	Mean: 24.5 Range: 19-42	M 83 (79%) F 22 (21%)	N/A	Healthy	18-g 20-g 22-g	Yes	15.0 (SD 3.3)	N/A	mmH2O	31 patients received sodium bromide
Fremont-Smith et al 1933	1,418	N/A	N/A	N/A	Diagnostic	N/A	N/A	13.2	12.0-14.9	mmCSF	

†Calculated from values provided, SD=Standard Deviation [7] [5] [16] [8] [9] [17] [10] [4] [3] [11] [12] [18]

Table 2: Summary of Findings for Normal CSF Opening Pressure

QUALITY ASSESSMENT

A quality assessment of the 12 identified studies was performed after data abstraction using a modified version of the NIH Quality Assessment Tool for Observational Cohort and Cross-Section Studies. Results of the quality assessment are provided in table 3.

	Fleischman et al 2012	Bø et al 2010	Bono et al 2009	Whiteley et al 2006	Edsbagge et al 2004	Bono et al 2002	Albeck et al 1991	Corbett et al 1983	Gilland et al 1974	Gilland 1969	Tourtellotte et al 1964	Fremont-Smith et al 1933
Was the research question or objective clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the subjects recruited from similar populations and time periods?	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were inclusion and exclusion criteria clear and uniformly applied to all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was a sample size justification, power description, or variance and effect estimates provided?	N	N	N	N	N	N	N	N	N	N	N	N
Was the analysis clear and appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the variables clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the outcome measures clearly defined and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was there blinding or another means of reducing bias clearly described?	N	N	Y	N	N	N	N	N	N	N	N	N
Were confounding variables measured and reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N

Y: Yes, N: No

Table 3: Quality Assessment of Eligible Studies

Chapter 5 Discussion

SUMMARY

This qualitative systematic review examined the normal range of cerebrospinal fluid opening pressure for adults as reported in the literature. Subjects included both healthy volunteers as well as patients undergoing diagnostic lumbar puncture who were not diagnosed with a condition that would affect ICP. A systematic review of the PubMed database was performed as well as manual search of reference lists from eligible full-text records and contributions from relevant experts. Of the 164 records screened, 39 full-text records were reviewed and ultimately 12 records meeting inclusion and exclusion criteria were included in qualitative data synthesis. Mean CSFOP values for each study are presented in Table 2 with SD where available. Mean CSFOP ranged from 12.98 to 18.8 cmH2O where reported. The overall range of CSFOP reported was 6 to 28 cmH2O for all 12 studies.

Six (50%) of the twelve studies identified in this systematic review indicate that the upper limit of normal for CSFOP may be greater than 20 cmH2O [7] [5] [8] [10] [4] [3]. Five of the included studies did not report normal subjects with CSFOP greater than 20 cmH2O, and one study did not provide information on the range of CSFOP [16] [9] [17] [11] [12] [18]. Of the studies performed in healthy volunteers, CSFOP ranged from 8 to 24 cmH2O. For the studies utilizing subjects without diagnoses affecting ICP in whom diagnostic LPs were performed, CSFOP ranged from 6 to 28 cmH2O. Given the findings of this qualitative review, a normal CSFOP range between 6 and 25 cmH2O as suggested in the most recent review article by Lee et al in 2014 would be supported [6].

Although the range of normal CSFOP may be greater than 20 cmH2O in some adults, the appropriate clinical cutoffs for further workup and diagnosis remain to be determined. Maintaining 20 cmH2O as the upper limit of normal in clinical settings may be beneficial in allowing for more sensitive screening for particular conditions. However, based upon the data presented in this review, caution should be taken in diagnosing asymptomatic individuals with a normal neurologic exam with a medical condition based upon CSFOP levels above 20 cmH2O alone.

The findings of this systematic review are of particular relevance to research or occupational surveillance programs in which a baseline CSFOP is required for comparison. Future work will include a quantitative meta-analysis, which will provide a more precise description of the normal range of CSFOP.

PUBLIC HEALTH IMPLICATIONS

The inspiration for this systematic review was to clarify a normal range of CSFOP to allow for interpretation of research data and data collected through future occupational surveillance of the astronaut population. However, the results of the systematic review have benefits both for the astronaut population as well as the general population. Lumbar punctures and ICP monitoring are performed throughout the US and globally in emergency rooms, ICUs, as well as outpatient neurology and neuro-ophthalmology settings. The interpretation of these results will be better informed by clearer definitions of normal physiologic ICP levels, allowing for more effective screening and diagnosis. Furthermore, elevated ICP has been noted in a number of terrestrial conditions on Earth including idiopathic intracranial hypertension, head trauma, aneurysm, brain masses, hydrocephalus, etc. Understanding the changes and remodeling of CSF spaces and pressures in spaceflight may have terrestrial correlations as well and improve our overall understanding of cerebrospinal fluid dynamics. Improved understanding of these principles may allow for improved prevention, diagnosis, monitoring, and treatment of these conditions in the future.

Strengths and Limitations

This systematic review provides a robust review of primary literature on the normal range of CSFOP in adults. The most recent review article by Lee et al in 2014 on the subject describes four papers, one of which includes the pediatric population. In comparison, this systematic review identified twelve studies with relevant data. All but one study provided by experts in the field were identified via database searching and cross-referencing. It was therefore felt that the search approach was effective at identifying relevant literature. Although broader database search syntax may have identified additional records for screening, the method of manually reviewing relevant full-text reference lists for additional records allowed for an efficient search of the literature. The research question of identifying a normal range of CSFOP lent itself to primarily observational studies including cohort and cross-sectional studies with descriptive analyses. A broad range in date of publication was purposefully included as clinical practice cutoffs for CSFOP are largely guided by older literature. For consistency and increased power, mean values for CSFOP and SD were calculated and listed for records containing multiple relevant subgroups. However, identifying subgroups with demographic characteristics more similar to the population of interest may be prudent. For instance, the study by Fleischman et al includes patients with ages from 20 to 95 years. The age 20 to 49, 50 to 54, and 55 to 59 age subgroups may be more relevant to the astronaut population.

Conclusions

This qualitative systematic review provides a description of the normal range of CSFOP available in the literature. A better understanding of the normal range of CSFOP will allow for better interpretation of research. Additionally, understanding the range of normal CSFOP may help guide clinical screening, diagnosis, and treatment. Specifically, for the astronaut population, the normal range of CSFOP in a terrestrial population will be useful for comparison of research and any future occupational surveillance. Future work will include working with the epidemiology team at NASA JSC to perform a meta-analysis of identified relevant literature in order to better quantify a normal CSF opening pressure range.

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