Growth and Resorption of Chronic Subdural Hematomas: Gardner, Weir, and the Osmotic Hypothesis Revisited

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■ BACKGROUND: **To explain why some chronic subdural hematomas (CSDHs) grow and/or resorb, a physically decreasing outer membrane (OM) surface area (SA) to CSDH volume (V) ratio has been reexplored, and a critical CSDH size inferred (OM SA ≈ V). Gardner showed that since CSDH protein exceeded cerebrospinal fluid (CSF) protein, CSF→CSDH osmosis occurred across a semipermeable inner membrane (n = 1). By contrast, Zollinger and Gross demonstrated that serum→CSDH osmosis could also occur across the OM (n = 1). Notably, Weir refuted Zollinger and Gross by finding equal CSDH and serum total protein (n = 20); however, Weir did not refute Gardner. Although all extant mechanisms, especially rehemorrhages, explain CSDH growth, only OM SA ≥ V simultaneously permits resorption. We aimed to reevaluate the osmotic hypothesis.**

■ METHODS: **Paired serum and CSDH samples were measured in a prospective cohort.**

■ RESULTS: **Results were consecutively obtained in 116 patients (87 men; mean age, 73 ± 13 years). Serum osmolality and CSDH osmolality were similar (285.70 ± 7.99 vs. 283.85 ± 7.52 mmol/kg, respectively; $P = 0.11$) and significantly correlated ($r = 0.75$, $P < 0.0001$). Serum total protein significantly exceeded CSDH total protein (66.6 ± 6.8 vs. 43.68 ± 20.24 g/L, $P < 0.0001$) as did serum albumin (35.62 ± 4.46 vs. 30.85 ± 8.5 g/L, $P < 0.0001$) and serum total globulins (31.5 ± 6 vs. 18.6 ± 11.4 g/L, $P < 0.0001$). Serum and CSDH proteins were not correlated (total protein: $r = 0.003$; albumin: $r = 0.08$; globulins: $r = 0.21$).**

■ CONCLUSIONS: **Only crystalloids equilibrated. CSDH colloids were significantly decreased. CSDH dilution or colloidal flocculation is implied. CSDH dilution (by CSF→CSDH inner membrane [IM] osmosis or OM transudation/exudation) could favor CSDH growth, as would repeated OM hemorrhages. Contrariwise, isolated colloidal flocculation could favor CSDH shrinkage by OM CSDH→serum osmosis. The latter may result in OM SA ≥ V favorable for ultimate resolution. Our results refute Weir and Zollinger and Gross, but not Gardner. Osmotic gradients simultaneously exist for both CSDH growth and resorption. Each equilibrium could depend on each gradient relative to each IM/OM semipermeability.**

INTRODUCTION

It is unknown why some chronic subdural hematomas (CSDHs) spontaneously resolve yet others inexorably grow. Physical mechanisms, such as a decreasing CSDH surface area (SA) to volume (V) ratio, with increased CSDH size, were originally suggested by Apfelbaum et al.[1] A critical size, beyond which CSDH growth became inexorable, was anticipated, but could not be determined.[1] However, Apfelbaum et al.'s hypothesis[1] has recently been reexplored, and the critical size is estimated to be when CSDH V exceeds the resorbing SA. Because of its thickness and complex of neo-macrocapillary sinusoids, compared with the thin avascular inner membrane (IM),[2-4] the resorbing surface was assumed to be the CSDH outer

Key words
- Chronic subdural hematoma
- Osmosis

Abbreviations and Acronyms
CSDH: Chronic subdural hematoma
CSF: Cerebrospinal fluid
IM: Inner membrane
OM: Outer membrane
SA: Surface area
V: Volume

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membrane (OM).[5] Therefore, the critical size was determined to be when CSDH V $\geq$ OM SA.[2]

By contrast, Gardner[6] had previously emphasized a purely chemical mechanism for CSDH growth. Because CSDH protein far exceeded cerebrospinal fluid (CSF) protein, Gardner hypothesized that CSF→CSDH osmotic ingress occurred across the arachnoid mater and CSDH IM,[6] which together acted as a semipermeable membrane. However, only the IM was strictly tested in his solitary case.[6] Zollinger and Gross[7] subsequently refuted this by demonstrating serum→CSDH osmosis across the OM; however, the IM was curiously not tested in their solitary case.[7] Putnam[8] emphasized Fremont-Smith's[9] prior concept that extravasated blood must break down into numerous smaller molecules "…with a manifold increase in osmotic pressure." Although Zollinger and Gross[7] incorporated this mechanism to explain their hypothesis (i.e., serum→CSDH osmotic ingress across the OM), they did not actually confirm it.

Unfortunately, Weir[10] subsequently refuted Zollinger and Gross by demonstrating that CSDH total protein actually equaled blood total protein in 20 paired serum CSDH samples. Indeed, Weir[10] also measured oncotic pressure, and demonstrated no significant difference between each paired sample. In these paired samples, oncotic pressure was clearly linearly associated with CSDH total protein.[10] Nevertheless, Weir[11] concluded that his landmark studies had provided "…no evidence either to support or refute the concept of an osmotic mechanism" for CSDH expansion. Therefore, Weir did not refute Gardner. Furthermore, Weir[11] also noted that no existing osmotic mechanism could simultaneously explain CSDH resorption.

Although all extant mechanisms currently explain CSDH growth, only the critical size hypothesis (i.e., OM SA $\geq$ V)[1,5] currently also permits resorption. We aimed to reevaluate the osmotic hypothesis with more rigorous statistical power, in a more representative CSDH group than in prior studies by comparing CSDH colloids with those in paired serum controls.

METHODS

CSDH and serum samples were obtained as part of a prospective single-center cohort study between April 2014 and June 2017. The setting was a tertiary neurosurgery referral center in a major regional public hospital. Patients were eligible if they were symptomatic with a computed tomography scan–proven CSDH deemed by the treating consultant neurosurgeon to require surgical evacuation. Exclusion criteria included patients less than 18 years of age,[12] patients with a ventriculoperitoneal shunt, and patients where both the clinical scenario and neuroimaging were more compatible with an acute subdural hemorrhage, pregnancy, central nervous system tumor, or infection. Participants or assenting relatives were approached by the researcher, and details of the proposed study were administered along with a detailed information sheet. The experimental protocol and informed consent were approved by the institutional review board, and all subjects gave informed consent. Relative assent was obtained from a next of kin, or family member, wherever patients were considered unable to consent for themselves.

Most patients underwent the same operative procedure (i.e., burr hole evacuation with saline irrigation for each CSDH).[13] However, all patients underwent subdural drainage for 48–72 hours. Serum samples were taken immediately prior to burr hole evacuation. CSDH samples were obtained immediately after opening the dura and OM, and before any saline irrigation. Prophylactic antibiotics were administered at surgery (2 g cefazolin), and all drains were antibiotic-impregnated (clindamycin and rifampicin [Bactiseal, Codman & Shurtleff, Inc., Raynham, Massachusetts, USA]). Patients were encouraged to lie flat until the drain was removed (usually between 48 and 72 hours); however, they could ambulate for toileting and so forth. Drain removal was dictated by drainage output, postoperative computed tomography scan appearances indicating adequate decompression, and clinical impression. With bilateral CSDH, CSDH samples were only taken from the side containing the largest CSDH. No patient received plasma-expanding agents.

A history of trauma (falls, head injuries—trivial or significant—or assaults) was specifically sought in every case as part of the admission process, and corroborated by a consensus between the patient (where Glasgow Coma Scale score = 15) or the patient's family and/or referring physician (Glasgow Coma Scale score <15). Postoperative neurologic and functional status was assessed by a consensus of medical and nursing staff, combined with physiotherapists and occupational therapists. Total CSDH V was estimated on computed tomography scan using the approximate XYZ/2 technique, accepting its tendency toward overestimation.[14]

CSDH and peripheral venous blood samples were centrifuged at 3000 revolutions/minute for 10 minutes, aliquoted, and then stored at −80°C until subsequent batch analysis. Assays were performed by one author (D. R.) who was blinded to the patient concerned. Serum was considered the appropriate sample for analysis for both the CSDH and serum total protein and albumin because it is free from any interferences that can be caused by anticoagulant preservatives contained in the collection tubes. Serum differs from plasma only by the process of clotting and therefore by the disappearance of fibrinogen in the coagulum. Because both CSDH and serum samples were collected into plain collection tubes, all protein concentrations were comparable.

Osmolality was measured on both CSDH and serum samples using freezing point depression measurement from an osmometer (Advanced Instruments model 3320 [John Morris, Chatswood, New South Wales, Australia]). Total protein and albumin analysis, on both CSDH and serum, was performed on a Beckman Synchron DXC (600i) (Beckman Coulter, Mount Waverley, Victoria, Australia) automated chemistry analyzer using Beckman Coulter reagents. Total protein >10 g/L was determined using a timed end point biuret method (Beckman Coulter Australia). Albumin was determined using a timed end point Bromocresol green method (Beckman Coulter Australia). Total globulins were inferred by subtracting the albumin concentration from the total protein concentration.

Statistical Analysis

Statistical analysis was performed using SPSS 23 (IBM Corp., Armonk, New York, USA). Normality of score distribution for dependent variables was examined using descriptive statistics. Homogeneity of variance was considered using the Levene test for

Table 1. Demographics and Colligative Properties

Variable	Value	*P* Value
Demographics		
Age, mean ± SD (years)	73 ± 13	
Male/female	87:29	
History trauma/fall (%)	87 (75)	
Time since history trauma/fall, mean ± SD (days)	32 ± 24	
CSDH volume, mean ± SD (mL)	113 ± 62	
Bilateral CSDH (%)	24 (21)	
Recurrences (%)	10 (9)	
Colligative properties		
Serum osmolality, mean ± SD (mmol/kg)	285.70 ± 7.99	0.11
CSDH osmolality, mean ± SD (mmol/kg)	283.85 ± 7.52	
Serum versus CSDH osmolality	$r = 0.75$	<0.0001
Serum total protein, mean ± SD (g/L)	66.6 ± 6.8	<0.0001
CSDH total protein, mean ± SD (g/L)	43.68 ± 20.24	
Serum albumin, mean ± SD (g/L)	35.62 ± 4.46	<0.0001
CSDH albumin, mean ± SD (g/L)	30.85 ± 8.5	
Serum total globulins, mean ± SD (g/L)	31.5 ± 6	<0.0001
CSDH total globulins, mean ± SD (g/L)	18.6 ± 11.4	
Serum versus CSDH total protein	$r = 0.003$	0.91
Serum versus CSDH albumin	$r = 0.08$	0.95
Serum versus CSDH globulins	$r = 0.21$	0.54

In combination with Gardner's data,[6] a mean solitary acute hemorrhage of 47 mL could, with unhindered cerebrospinal fluid osmotic dilution, yield a CSDH volume of 113 mL by 32 days.
CSDH, chronic subdural hematoma.

equality of variance. For parametric data, analysis of variance was performed with statistical significance determined as $P < 0.05$. Statistical significance was determined at $P < 0.05$. Correlation between continuous variables was assessed with Pearson correlation, with statistical significance determined at $P < 0.05$. All data are given as mean ± SD.

Sample Size Calculation. In Weir's samples,[10] the total protein in blood was 66.0 ± 2.0 g/L compared with 65.0 ± 4.0 g/L in CSDH fluid. Assuming a required difference of 2.5 g/L, a sample size of approximately 100 paired samples would be required to demonstrate statistical significance at alpha of 0.05 with 85% power.[15]

RESULTS

Results were obtained in 116 patients (87 men; mean age, 73 ± 13 years; time since trauma or fall, 32 ± 24 days; CSDH V: 113 ± 62 mL) (Table 1). All clotting factors were exhausted in both CSDH and serum through the clotting process (which is not inhibited by an anticoagulant, as with plasma collection). Excessive lipids or hemolysis, which could potentially interfere with total protein analysis, were not observed. Extensive data regarding preoperative comorbidities and outcomes from the same cohort have been previously published.[13]

Serum osmolality and CSDH osmolality were similar (285.70 ± 7.99 vs. 283.85 ± 7.52 mmol/kg, respectively; $P = 0.11$) and were strongly correlated ($r = 0.75$, $P < 0.0001$) (Figure 1A and Table 1). Serum total protein (66.6 ± 6.8g/L) and serum albumin (35.62 ± 4.46 g/L), respectively, significantly exceeded CSDH total protein (43.68 ± 20.24 g/L, $P < 0.0001$) and CSDH albumin (30.85 ± 8.5 g/L, $P < 0.0001$) (Table 1). Serum total globulins markedly exceeded CSDH total globulins (31.5 ± 6 vs. 18.6 ± 11.4 g/L, respectively; $P < 0.0001$) (Table 1). Indeed, serum globulins were reduced to a far greater degree (41% reduction) than albumin reduction (14% reduction) ($P < 0.01$) (Table 1).

CSDH total protein and serum total protein ($r = 0.003$, $P = 0.91$), CSDH albumin and serum albumin ($r = 0.08$, $P = 0.95$), and CSDH globulins and serum globulins ($r = 0.21$, $P = 0.54$) were not correlated (Figures 1B–1D). CSDH total protein and albumin were significantly less in those with recurrences ($P = 0.029$ and $P = 0.041$, respectively) (Table 2); however, small recurrence rates ($n = 10$) precluded reliable analysis with sufficient power. A trend existed ($P = 0.061$) demonstrating poorer outcomes (modified Rankin Scale score) in those presenting with greater CSDH V (Table 2). Although statistically significant, correlations between CSDH V and CSDH total protein ($r = 0.201$, $P = 0.05$) and between CSDH V and CSDH osmolality ($r = 0.227$, $P = 0.026$) were weak and of limited clinical value.

DISCUSSION

Unlike prior landmark studies,[10,11] paired samples were obtained in our study from a representative group undergoing CSDH surgery. Notably, patients in Weir's study[10] were significantly younger than usual for CSDH (mean age, 48 years; range, 17–82 years). By contrast, the mean age in our sample was 73 ± 13 years. Furthermore, our study was also demonstrably adequately powered. In Weir's study, osmolality samples were randomly selected from 23 patients,[11] whereas protein samples were studied from 20 patients.[10] The studies of Zollinger and Gross[7] and Gardner[6] were even less statistically satisfactory: each was based on only a single patient, respectively. In our study, paired samples were obtained from 116 patients in a prospective, consecutive cohort.

As in the Weir study,[11] serum osmolality in our study did not significantly differ from CSDH (Table 1). Paired osmolalities were also significantly correlated (Figure 1A). Crystalloids therefore significantly equilibrated between serum and CSDH. By contrast, paired CSDH and serum samples for total protein, albumin, and globulins were not correlated (Figures 1B–1D and Table 1). Therefore, in marked contrast with crystalloids, colloids were not equilibrated. Colloidal osmotic pressures would therefore be expected to significantly differ between CSDH and CSF, and between CSDH and serum.

Although serum total protein in our study was almost identical to that of Weir,[10] CSDH total protein was significantly reduced (Table 1). CSDH total colloids were therefore significantly reduced compared

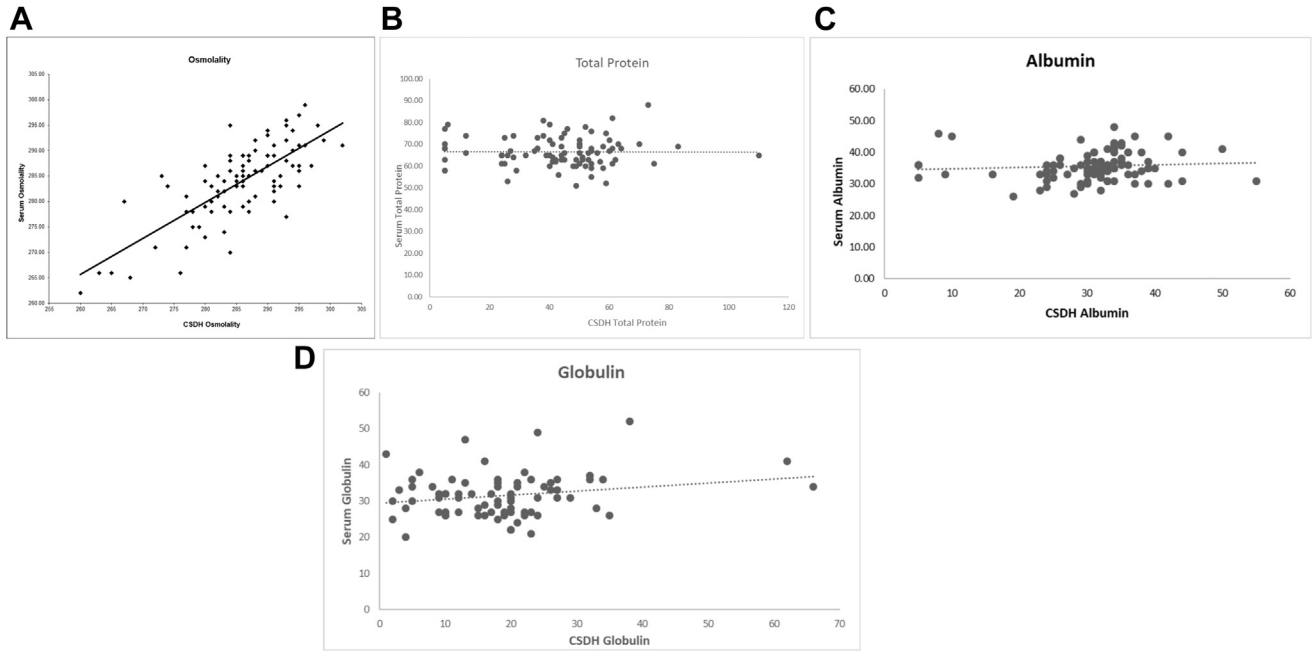

Figure 1. (**A**) Serum versus chronic subdural hematoma (CSDH) osmolality. Serum osmolality and CSDH osmolality were markedly similar and significantly correlated ($r = 0.75$, $P < 0.0001$). (**B**) Serum versus CSDH total protein. Serum total protein was significantly greater than CSDH total protein, and these were not correlated ($r = 0.003$, $P = 0.91$). (**C**) Serum versus CSDH albumin. Serum albumin significantly exceeded CSDH albumin, and these were not correlated ($r = 0.08$, $P = 0.95$). (**D**) Serum versus CSDH globulins. Serum total globulins were markedly greater than CSDH total globulins, and these were not correlated ($r = 0.21$, $P = 0.54$).

with serum. This refutes Weir,[10] and the premise of Zollinger and Gross.[7] Although CSDH albumin was significantly reduced compared with serum in our study, CSDH total globulins were significantly reduced to a markedly greater degree than serum total globulins. Interestingly, Weir[10] also found (equivalent total protein notwithstanding) that CSDH albumin was significantly reduced compared with blood (27.0 ± 30 vs. 38 ± 20 g/L, respectively; $P < 0.001$). However, this result was not discussed.[10] Furthermore, because CSDH and serum total protein were both similar in Weir's cases,[10] this suggests that CSDH total globulins were, by contrast,

Table 2. Specific Colligative Properties

	CSDH Fluid				
Clinical Parameter	**Total Protein**	**Albumin**	**Globulins**	**Osmolality**	**CSDH Volume**
CSDH volume	$r = 0.201$ $P = 0.050$ n = 95	$r = 0.166$ $P = 0.105$ n = 96	$r = 0.160$ $P = 0.156$ n = 79	$r = 0.227$ $P = 0.026$ n = 95	
mRS score, good (0–2)	44.16 ± 19.62	31.78 ± 7.76	17.85 ± 11.43	285.58 ± 7.14	103.91 ± 54.13
mRS score, bad (3–6)	42.80 ± 20.54 $P = 0.741$	30.02 ± 9.17 $P = 0.309$	18.61 ± 11.67 $P = 0.769$	286.57 ± 9.00 $P = 0.550$	124.42 ± 61.86 $P = 0.061$
Recurrences, yes	29.77 ± 19.89	25.44 ± 10.95	13.33 ± 10.36	287.11 ± 6.11	110.59 ± 37.17
Recurrences, no	44.93 ± 19.55 $P = 0.029$	31.48 ± 8.05 $P = 0.041$	18.63 ± 11.54 $P = 0.280$	285.94 ± 8.23 $P = 0.680$	113.99 ± 60.72 $P = 0.850$

Correlations between colligative properties and some clinical parameters are shown. Values are mean ± SD or as otherwise indicated.
CSDH, chronic subdural hematoma; mRS, modified Rankin Scale.

increased. If so, this is also contrary to our findings, and it was also not discussed.[10]

Decreased CSDH colloids imply colloidal flocculation/coagulation or CSDH dilution. They are subsequently discussed.

CSDH Colloidal Flocculation/Coagulation

Colloidal flocculation/coagulation results in protein sedimentation. This leaves a supernatant which is more dilute, and therefore less osmotically active, than the original fluid. If responsible, then flocculation occurred to a far greater degree with globulins (41% reduction) than with albumin (14% reduction) (**Table 1**). In our study, CSDH also invariably contained clots with consumed clotting factors. Such consumption also dilutes the supernatant, and represents a frequently cited mechanism for continued CSDH growth (i.e., by hyperfibrinolytic hemorrhage).[16] Notwithstanding, similar to most extant mechanisms, it does not per se explain spontaneous CSDH resolution.

CSDH Dilution

Two different mechanisms, operating through either the OM or IM, are implied. Therefore, CSDH dilution could occur by OM transudation (total protein <25 g/L) or exudation (total protein >25 g/L).[17] Despite having noted generally reduced CSDH albumin, Weir[10] also acquiesced that CSDH may contain "…an effusion of albumin-rich fluid." Rabe et al.[18] demonstrated that CSDH albumin is derived from circulating plasma, and not from CSDH red cell breakdown, as had previously been repeatedly assumed.[8,9] Indeed, Rabe[18] demonstrated that the total protein available from CSDH red cell breakdown could only constitute 1% that of serum albumin capillary turnover. **Figure 1B** shows that most CSDH in our sample would constitute exudate. Indeed, transudation appears incompatible with a preponderance of low pressure OM neocapillary sinusoids.[2-4] Exudation could potentially explain recurrences because CSDH total protein and albumin were significantly reduced here (**Table 2**). However, given only 10 recurrences, statistical analysis here is unreliable with insufficient power. Unfortunately, OM transudation/exudation could not readily explain CSDH resorption.

An alternative source of CSDH dilution is Gardner's osmotic hypothesis.[6] Therefore, although reduced compared with serum, CSDH colloids remain grossly elevated compared with CSF protein. Indeed, Weir[10] found that paired lumbar CSF protein was almost 100-fold less (i.e., 0.77 g/L). Moreover, ventricular or cisterna magna CSF protein would be even less still.[19] A large CSF→CSDH osmotic gradient therefore potentially exists. However, Zollinger and Gross[7] refuted this as a mechanism for CSDH growth because "…ordinarily, CSF does not pass through the arachnoid into the subdural space." Unfortunately, because it is now known that the subdural space does not normally exist (it is not anatomic, but always pathologic[20,21]), no subdural space containing fluid ordinarily exists with which to exert any osmotic effect. Therefore, the alternative mechanism proposed by Zollinger and Gross[7] was, in retrospect, unnecessary. A continued Gardner dilution[6] after surgical drainage could also explain recurrences.

Notably, β-trace protein measurement suggests that CSF penetrates into CSDH in most cases.[22] Interestingly, Gardner[6] demonstrated that 17 cm^3 of CSDH, enclosed by IM and placed within 52 cm^3 of paired CSF, increased in V by 2.9% over 16 hours. Because only crystalloids had crossed the IM, the IM had acted as a semipermeable membrane.[6] Such small increases have always been used to dismiss Gardner's hypothesis. However, combining Gardner's data with ours, a mean solitary acute hemorrhage of 47 mL could, with unhindered Gardner-type dilution, yield a hypothetical initial CSDH V of 113 mL by 32 days (i.e., the mean values that we observed) (**Table 1**). This potentially supports Gardner's hypothesis and could readily account for the hypodense CSDH commonly observed on computed tomography scan. Interestingly, the inferred initial V (i.e., 47 mL) is strikingly close to that based on OM SA to V ratio measurements (i.e., 48 mL), which otherwise augured for CSDH resolution.[5]

Proposed Mechanism for CSDH Growth and Resorption

Importantly, Gardner's mechanism,[6] as with all mechanisms (excepting that of the OM SA to V ratio[5]), only potentially explains CSDH growth. It neither explains spontaneous CSDH resorption nor invariable resorption after surgery. Indeed, as Weir[11] observed, "…one would have to postulate a reverse phenomenon." Interestingly, such a reverse phenomenon is possible because the high intra-CSDH compartmental pressures frequently observed at surgery could, at least theoretically, effect reverse osmosis. Unfortunately, however, direct reverse osmosis could not explain continued CSDH resorption after surgery, where intra-CSDH pressures have typically markedly fallen (with gas frequently present on computed tomography scan). Indeed, low intra-CSDH pressures would perhaps especially apply with sustained postoperative subdural drainage, the current criterion standard treatment.[23]

By contrast, our study is the first to provide a potential osmotic mechanism for both the growth and resorption of CSDH. This would complement the physical mechanism associated with an OM SA to V ratio.[1,5] Because CSDH is hyperosmotic to CSF, but simultaneously hypo-osmotic to serum, 2 competing gradients potentially exist: one across the IM, the other across the OM. Although colligatively greater across the IM, IM and OM semipermeability could differ and potentially override colligative effects. Osmotic equilibria would therefore depend on the magnitude of each gradient relative to IM/OM semipermeability. Therefore, wherever the IM is more semipermeable, CSDH might grow, appear hypodense on computed tomography scan, and potentially explain recurrences (**Table 2**). By contrast, wherever the OM is more semipermeable, CSDH might shrink to OM SA > V to then favor resorption.[1,5] Notwithstanding, rehemorrhages[16] and/or exudation[17] could overwhelm purely osmotic equilibria, and elicit inexorable CSDH growth and recurrences. As Weir[11] pragmatically acknowledged "…it is unlikely that there is a…single mechanism for the development of CSDH."

Management Options

Our results potentially have some implications for treatment. Flushing CSDH at surgery, by further diluting colloids, could increase a favorable CSDH→serum OM osmotic gradient, and

decrease an unfavorable IM→CSDH gradient. Increased serum osmolality (e.g., by infusing mannitol, as Bender and Christoff[24] used in his classic series of conservatively managed CSDH) could also enhance resorption. However, given excess comorbidities,[13] and excess postoperative morbidity[13] in an already aged population,[13,23] systemic fluid treatment should be advocated only with extreme caution in CSDH. Finally, if validated with larger numbers, and with validated cutoffs, CSDH fluid protein analysis could help to predict recurrences where total protein and albumin concentrations appear abnormally low, with this potentially indicating either ongoing Gardner's dilution or OM exudation.

Limitations

In our study, unlike the Weir study,[10] we did not additionally measure oncotic pressures. However, although the latter might seem to represent the more appropriate biological parameter, the use of oncometers has greatly diminished since the Weir study. This may be because total protein and especially albumin are closely correlated with oncotic pressures[10,25] and are far easier to measure. However, the clinical utility of oncotic pressures, as derived from oncometers, has also been questioned. For example, Duncan and Young[25] found that pulmonary edema was not correlated with oncotic pressures as derived from an oncometer. Notwithstanding, future studies could incorporate oncotic pressures, as in the Weir study.[10]

CONCLUSIONS

Our results refute Weir and Zollinger and Gross, but not Gardner. Osmotic mechanisms could influence both CSDH growth and resorption. Repeated OM hyperfibrinolytic hemorrhages, or exudates, only explain CSDH growth. The OM SA to V ratio and osmosis may act together to influence CSDH natural history.

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