

Systematic Overview of the Evidence Supporting the Use of Cerebrospinal Fluid Drainage in Thoracoabdominal Aneurysm Surgery for Prevention of Paraplegia

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POSTOPERATIVE paraplegia resulting from spinal cord ischemia is a devastating complication of thoracic aneurysm (TA) or thoracoabdominal aortic aneurysm (TAAA) surgery. Permanent neurologic deficits are a major cause of morbidity and may shorten long-term survival.^{1,2} Factors that are associated with the development of paraplegia are previous aortic surgery, preoperative renal function, age, aortic cross-clamp time, and emergency repair.^{3,4} The risk of injury also is significantly greater after repair of more extensive aneurysms.³ Aneurysms traditionally are classified by their extent and location (table 1).² At greatest risk is the patient with an aneurysm involving most or all of the thoracic and abdominal aorta (Crawford type II).^{2,3,5}

Strategies proposed to protect the spinal cord during TAAA repair aim to maintain spinal cord perfusion.⁶⁻⁸ Aortic occlusion increases cerebrospinal fluid pressure (CSFP) and decreases distal aortic systolic pressure, thereby decreasing perfusion of the spinal cord. Theoretically, decreasing CSFP by cerebrospinal fluid drainage (CSFD) should improve spinal cord blood flow and decrease the risk of spinal cord ischemic injury. Indirect evidence from canine models showing improved neurologic outcome using CSFD in spinal cord ischemia was first reported by Blaisdell and Cooley.⁶ Despite improvements in neurologic outcome in other animal models,^{7,9,10} no prospective, randomized trial has demonstrated any benefit of CSFD alone in humans undergoing aortic aneurysm repair. The purpose of this article is to provide a systematic review of the literature on the use of CSFD in humans undergoing surgical repair of the TAAA.

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Methods

Literature Search

A computerized MEDLINE search from 1966 to March 1999 was conducted using the Medical Subject Heading "aortic aneurysm, thoracic," with subheading "surgery." This was combined with the headings "paraplegia" and/or "cerebrospinal fluid." A second MEDLINE search using the text words "aortic aneurysm" and "cerebrospinal" combined with "and" was also conducted from 1966 onward. The reference lists of all relevant articles were examined and additional relevant citations were identified and retrieved. The Science Citation Index was also searched from January 1989 to December 1997 using the terms "thoracic aneurysm" or "thoracoabdominal," and yielded no additional references. The "Thoracic Aorta" chapter in *The Yearbook in Vascular Surgery* series from 1992 through 1998 was also reviewed for any related articles.^{10A,10B} These were retrieved and their citations checked for relevant articles. Finally, four vascular surgeons at McMaster University were contacted to identify any published or unpublished work in this area that may have been missed by the electronic and manual searches.

Selection Criteria

To avoid selection bias, articles were reviewed independently by two observers who were blinded to the authors, institution, journal of publication, year of publication, and results of the article. Disputes were resolved by consensus. The criteria for eligibility were determined *a priori*. Research was eligible for inclusion if it met the criteria listed below.

1. Target population: humans undergoing elective or emergent TA or TAAA surgery
2. Therapeutic intervention: intraoperative CSFD for spinal cord protection
3. Outcome: postoperative neurologic deficits (paraplegia or paraparesis)
4. Study design: randomized controlled trials, nonrandomized trials with concurrent controls, nonrandomized trials with historical controls, and case series

Case reports were excluded.

Table 1. Crawford's Classification of Thoracoabdominal Aneurysms

Group	Location and Extent of Aneurysm
Type I	Most or all of the descending thoracic aorta to the celiac artery
Type II	Most or all of the descending thoracic and abdominal aorta
Type III	Most or all of the distal descending thoracic and abdominal aorta
Type IV	Most or all of the abdominal aorta up to and including the celiac artery

Validity Assessment

The methodologic quality of the studies was assessed independently by both authors, who were blinded to the authors, institution, journal of publication, year of publication, and study results. Separate criteria were established *a priori* for each type of study design. For randomized controlled trials, items assessed included allocation of subjects (true randomization *vs.* pseudorandomization), specification of inclusion and exclusion criteria, blinding of outcome, and patient follow-up. For observational cohort studies, items assessed were design (retrospective or prospective), method of patient selection, recruitment strategy, similarity of baseline demographics among groups, comparability of confounders, blinding assessment of outcome, documentation of cointervention, and patient follow-up. Studies with historical controls were assessed using the same items as the observational cohort studies, except that the first two items were omitted.

Table 2. Outcome Data According to Level of Evidence

Reference	Design	CSFD	Confounders	Crawford Type I/II/III/IV/TA	Outcome Blinded	Advocate CSFD
Crawford et al., 1990 ¹	RCT	< 50 ml	No	19/27/0/0/0 (C) 25/27/0/0/0	Yes	No
Svensson et al., 1998 ¹⁵	RCT	< 10 mmHg + papavarine	Yes	13/4/0/0/0 (C) 11/5/0/0/0	Yes	Yes
Svensson et al., 1988 ¹⁶	OCS	5–15 mmHg + papavarine	Yes	—	—	No
Acher et al., 1994 ¹⁷	OCS	< 10 mmHg + naloxone	Yes	10/14/6/7/0 (C) 9/19/6/15/0	—	Yes
Acher et al., 1998 ¹⁸	OCS	? + naloxone	Yes	—	—	Yes
Acher et al., 1990 ¹⁹ (subset of Acher, 1994 ¹⁷)	NRHC	< 14 mmHg + naloxone	Yes	5/8/5/3/2 (C) 4/8/5/3/4	—	Yes
Murray et al., 1993 ²⁰	NRHC	< 15 mmHg	Yes	8/14/17/0/11 (C) 15/4/6/0/23	—	No
Hollier et al., 1992 ²¹	NRHC	< 10 mmHg	Yes	7/13/16/6/0 (C) 22/16/23/47	—	Yes
Safi et al., 1998 ²²	NRHC	< 10 mmHg	Yes	—	—	Yes
Safi et al., 1994 ⁴	Case	< 15 mmHg	Yes	14/31/0/0/0	Yes	Yes
Svensson et al., 1990 ⁸	Case	5–15 mmHg < 50 ml + papavarine	Yes	5–Type I or II 6–TA	—	No
Safi et al., 1996 ²⁴ (45 patients from Safi 1994 ⁴)	Case	< 10 mmHg	Yes	31/63/0/0/0	Yes	Yes
Cambria et al., 1989 ²⁵	Case	Unspecified	Yes	—	—	No

(C) = control group; Case = case series; CSFD = cerebrospinal fluid drainage; NRHC = nonrandomized historical cohort; OCS = observational cohort study; RCT = randomized controlled trial; TA = thoracic aneurysm.

Data Extraction

After the validity assessments were completed, the articles were unblinded and data were extracted independently in duplicate by both authors. Data were summarized in tables to facilitate qualitative assessment and data extraction.

Results

Study Selection

The initial MEDLINE search yielded 121 articles, of which six met the inclusion criteria. The second MEDLINE and Science Citation Index searches identified two possible additional references, but both failed to meet the inclusion criteria. Nineteen additional articles were identified through the citations from relevant articles, and eight of these met the inclusion criteria. One study was excluded after the data extraction phase because CSFD was used in eight patients of the protocol group, but data could not be obtained specifically on those patients.¹¹ A total of 13 articles were identified for this overview (table 2). No review articles were identified through the search process. Analysis of agreement between observers on article inclusion based on selection criteria was calculated using weighted κ statistics and was found to be 0.70. A kappa score between 0.6 and 0.8 was considered to be good agreement. All disputes were resolved easily by consensus and were the result of oversight in all cases.

Study Outcomes

The studies that met the inclusion criteria are presented in table 2 and are ranked according to the strength of the level of evidence. These included two randomized controlled trials, three nonrandomized observational cohort studies, four nonrandomized historical controls, and four case series. Data from the trials were not statistically pooled in a meta-analysis due to the heterogeneity in methodologic design.¹²⁻¹⁴ Methodologic deficiencies that weaken the strength of evidence will be discussed within each group of study design.

Randomized Controlled Trials. The prospective randomized controlled trial by Crawford *et al.*,¹ which stratified high-risk type I and II TAAAs, failed to demonstrate a reduction in neurologic deficits using CSFD. The incidence of neurologic deficit was 30% (14 of 46) in the CSFD group and 33% (17 of 52) in the controls ($P = 0.80$). Groups were matched for use of atriofemoral bypass and reattachment of intercostal and lumbar arteries. In this study, CSFD was limited to 50 ml and in only 20 of 46 patients was CSFP reduced to less than 10 mmHg.

Svensson *et al.*¹⁵ conducted the most recent prospective randomized controlled trial on patients undergoing Crawford type I or II TAAA surgery. The methodology included a planned interim analysis of the data for safety and efficacy, which resulted in early termination of the study after enrollment of 33 of 66 eligible patients (their *a priori* sample size was 100 for $\alpha = 0.05$ and power = 20%). The intervention consisted of a combination of CSFD and intrathecal papaverine. Cerebrospinal fluid (CSF) was allowed to drain freely during aortic cross-clamping and was stopped after unclamping. Intrathecal papaverine was instilled before cross-clamping. Postoperatively, CSF drained freely for CSFP greater than 10 cm H₂O. Other possible spinal cord protective measures included distal aortic perfusion (DAP) using atriofemoral bypass, aortic segments sequentially repaired to maintain proximal and distal perfusion, and segmental artery reattachment; these were equally distributed between the two groups. However, in the group of patients with normal outcome, the use of active cooling using bypass was higher (16 of 24) compared with the group with postoperative neurologic injury (2 of 7; $P = 0.02$). Aortic cross-clamp times were also longer (32.3 ± 15.1 vs. 50.3 ± 19.3 min; $P = 0.008$) in the group with neurologic deficits. Neurologic outcome evaluation was graded by a blinded neurologist. Overall neurologic deficit rates were 2 of 17 (12%) in the CSFD and papaverine group compared with 7 of 16 (44%) in the control group ($P = 0.039$). They concluded that the combination of CSFD and intrathecal papaverine significantly reduced the incidence and severity of neurologic injury, and this effect was additive if combined with atriofemoral bypass with hypothermia. The study was terminated early because a statistically significant difference was reached after one third of the patients had been entered. The

authors stated that, "if the study had continued, the difference probably would have become stronger, but it may also not have been borne out in a larger series." The issue of early termination in this study is discussed further in the Discussion.

Nonrandomized Observational Cohort Studies. Three nonrandomized observational cohort studies met the eligibility criteria.¹⁶⁻¹⁸ Svensson *et al.*¹⁶ conducted their prospective study in two countries (South Africa and the United States) at different time periods. Baseline comorbid disease was not described. It was not stated whether patients were selected consecutively or whether outcome assessment was blinded. The intervention consisted of intrathecal papaverine and CSFD. During the study, the CSF drainage protocol was changed. Initially, CSF drained freely, but later, volume was restricted to 50 ml. In addition, more patients in the control group had intraoperative shunts or femoral-femoral bypass. Although their results were not statistically significant, they concluded that intrathecal papaverine protected the spinal cord during aortic cross-clamping. No conclusions were drawn regarding the concomitant use of CSFD.

Acher *et al.*¹⁷ published a retrospective observational cohort study using consecutive patients in 1994. This study included the data from the 47 patients in their previously published study in 1990.¹⁹ Combined CSFD and intravenous naloxone was used in the intervention group ($n = 61$). Three different protocols were used in the control group ($n = 49$): 13 patients received only CSFD; eight received only naloxone; and 28 received neither. Type of aneurysm repair, cross-clamp times, pre-morbid risk, and surgical technique were distributed equally among groups. Overall neurologic deficit rates were 1 of 61 (1.6%) in the CSFD and naloxone group, and 11 of 49 (22.4%) in the heterogeneous control group ($P < 0.001$). They developed a formula to predict the risk of neurologic deficit and concluded that combined use of CSFD and naloxone protected against neurologic deficits.

In 1998, Acher *et al.*¹⁸ conducted a prospective cohort study using 217 consecutive patients undergoing TAAA (all types) and TA surgery from 1984 through 1996 and studied preoperative and operative factors for paraplegia risk and survival. Surgical technique included simple aortic cross-clamping without assisted circulation, moderate hypothermia, renal cooling, and intercostal ligation with no intercostal reimplantation. The intervention consisted of CSFD and low-dose naloxone. It was not stated whether CSFD was pressure or volume limited, how long it was used, or if neurologic outcome assessment was blinded. There were 5 of 147 (3 deaths) neurologic deficits in the CSFD and naloxone group, compared with 12 of 58 (9 deaths) patients with deficits in the group without CSFD and naloxone. Using a mathematical model of paraplegia risk, they evaluated 80 potential risk

factors for paraplegia and based their expected paraplegia rates in the two groups by using their previously developed formula.¹⁷ Using univariate analysis, they identified nine significant preoperative and operative factors for paraplegia risk. Several mathematical models were then created using logistic regression to investigate the interaction of these variables, and it was concluded that paraplegia risk correlated with the amount of aorta replaced, acute dissection, temperature before aortic occlusion, volume replacement, blood oxygen level, aortic occlusion time and cardiac index. They also concluded that with CSFD, naloxone administration, and early ligation of intercostal arteries without reimplantation, the estimated risk of paraplegia was one seventh that of graft inclusion and intercostal reimplantation with or without assisted circulation.

Nonrandomized Historical Controls. Four studies in this category met the eligibility criteria¹⁹⁻²² and are presented in no special order.

Acher *et al.*¹⁹ compared 23 patients using CSFD to maintain CSFP lower than 14 mmHg against 24 historical controls over a 5.5-yr period. Twelve patients in the CSFD group also received intravenous naloxone for 48 h postoperatively. We could not identify if the distribution of comorbid disease was similar in the study groups, although both groups were comparable in terms of type of aneurysm, cross-clamp time, presence of dissection, and intraoperative technique. The incidence of neurologic deficits was 1 of 23 in the intervention group and 7 of 24 in the control group ($P < 0.03$). The authors support the use of both naloxone and CSFD, although their relative contribution in reducing neurologic deficits cannot be determined.

Murray *et al.*²⁰ did not demonstrate improved neurologic outcome using CSFD to keep CSFP lower than 15 mmHg. Groups were demographically similar except for extent of aneurysmal disease; the control group had primarily TAs, whereas the intervention group had more diffuse high-risk type II aneurysms (14 of 50 *vs.* 4 of 49; $P < 0.05$) and type III aneurysms (17 of 50 *vs.* 6 of 49; $P < 0.05$). This reflected the changing nature of the surgical practice in that institution. Although not statistically significant, intraoperative bypass (9 of 49 *vs.* 4 of 50) and shunts (14 of 49 *vs.* 12 of 50) were used more frequently in the control group. Another difference between the groups was the use of mild hypothermia (passive cooling to 34°C) in the intervention group. The volume of CSF removed ranged from 3 to 150 ml, and the range of CSFP while cross-clamped was 9.4 to 13.3 mmHg. There were technical difficulties withdrawing CSF in six patients, in whom CSFPs were greater than 15 mmHg.

Hollier *et al.*²¹ described a multimodal protocol in the intervention group to reduce neurologic complications in a nonrandomized historical control study. The protocol included CSFD up to 3 days postoperatively, avoiding solutions containing glucose, passive hypothermia, a bo-

lus of thiopental sodium before cross-clamp, use of mannitol and nimodipine, reattachment of intercostal arteries, and expeditious surgical technique to minimize spinal cord ischemia. There were no spinal cord deficits in the protocol group (0 of 42) and 6 of 108 in the nonprotocol group, but CSFD was used in three patients in the nonprotocol group. Intraoperative details are provided for the protocol group, but none are provided for the nonprotocol group.

Safi *et al.*²² examined the effect of cross-clamp time greater than 30 min in all patients with TAAA or TA over a 5-yr period. Of 370 patients, 280 met this criterion and 111 had type II TAAAs. There were nine intraoperative deaths, yielding 271 survivors of whom 112 underwent simple cross-clamp repair and 159 had the adjuncts of DAP (left atrial to femoral bypass) and CSFD. The rationale of DAP is that by increasing distal aortic pressure and decreasing proximal hypertension, perfusion to the spinal cord will increase, providing protection during the time of aorta cross-clamping.²³ Contraindications to CSFD, as stated by the authors, included previous operation on the spinal cord or blood effusion; the latter is not further defined. In some instances, emergent surgery prevented catheter insertion. It was not stated how many patients in the CSFD group did not receive CSF catheters because of these reasons. CSFP was maintained lower than 10 mmHg for up to 4 days postoperatively. Patient temperature was allowed to drift to 33°C. Neurologic deficit occurred in 23 out of 271 patients; nine patients died. For highest-risk type II TAAAs, the neurologic deficit rate was 11 of 29 (38%) for cross-clamp *versus* 6 of 82 (7.3%) for those with DAP and CSFD. This was stated in the body of their article, as data was presented as a function of cross-clamp time and risk factors for neurologic deficit and not by the intervention of CSFD and DAP. They concluded that perioperative CSFD and DAP had great impact in preventing neurologic deficit, most significantly in type II TAAAs.

Case Series. Four case series were identified that met the inclusion criteria and are listed in no special order.^{4,8,24,25}

Safi *et al.*⁴ prospectively evaluated and reported combined CSFD and DAP using atriopoplasmic bypass in 45 consecutive patients with high-risk type I and II TAAAs. In this series, CSFD was used to reduce CSFPs to less than 15 mmHg. Two patients awoke with paraplegia (one had an intraoperative cardiac arrest), and two patients developed delayed paralysis. The range of CSF drained was 5 to 80 ml intraoperatively and 0 to 698 ml postoperatively. Median aortic cross-clamp time was 42 min, and pump time ranged from 12 to 87 min. The incidence of paraplegia (two early and two delayed) in this group was then compared with a historical control group of 112 patients from their center, of whom 26% had DAP. Another cohort of 98 randomized patients from a previous study at their center¹ was originally

chosen for the control group, but because of their significantly higher incidence of neurologic deficit (32%), they decided to use the more recent cohort of 112 patients. However, this more recent cohort had a similar incidence of neurologic deficit (31%); therefore, it is unclear what their rationale was in their criteria for selecting the control group. It is methodologically unsound to choose a control group *post hoc* in this fashion. These data were therefore presented as a case series.

Svensson *et al.*⁸ retrospectively reported a case series of 11 patients who underwent TA or TAAA surgery. CSFD was used to withdraw 20 ml of CSF when the pleural cavity was opened. Before aortic cross-clamping, intrathecal papaverine was instilled via the CSF drainage catheter. CSF was allowed to drain freely during the period of aortic cross-clamping. Unfortunately, this protocol changed during the series, and the total volume of CSF removed was limited to 50 ml in later patients. The change in CSFD protocol is similar to that described in their previous study.¹⁶ There were no instances of postoperative paraplegia, but one patient developed delayed paraparesis.

Safi *et al.*²⁴ reported in 1996 another case series of 94 patients with type I and II TAAA treated with CSFD and DAP. However, this series included the data from the 45 patients previously published in 1994.⁴ Approximately one half of the patients had CSF pressures maintained at 10 to 15 mmHg, whereas the remaining had CSF pressures maintained at less than 10 mmHg. Eight of the 94 patients developed paraplegia or paraparesis postoperatively (five early and three delayed). The authors compared their results with those of a control group of 42 patients who did not receive CSFD or DAP; however, it is not stated whether the control group represents a consecutive historical cohort or these patients were chosen randomly. Additionally, the control group is described in the abstract as consisting of type I and II TAAAs, but in the manuscript as type I and III TAAAs. If the latter is true, the groups differ and have dissimilar risks for developing neurologic complications.

Cambria *et al.*²⁵ report their recent experience over a decade with 55 patients undergoing TAAA repair. During that period, the surgical protocol changed to include the Crawford inclusion technique, and therefore patients were divided into two groups for analysis (earlier group 1 = 26; later group 2 = 29). CSFD was used only in the final 15 patients of group 2. None of these patients with CSFD received shunts or bypass intraoperatively, and intercostal arteries were not consistently implanted. The type of aneurysm and comorbidity were unspecified, but there were no neurologic deficits postoperatively. CSFD was pressure limited, but the pressure limit was not specified. Over time, they found a significant reduction in operative mortality, total operative time, blood loss, and aortic cross-clamp times. Given the small number of patients with CSFD, the authors draw no

conclusions on the influence of CSFD on spinal cord deficit.

Discussion

This article provides a systematic review of the published literature on the evidence supporting the use of CSFD in TAAA surgery for prevention of paraplegia. We followed rigorous methodologic strategies that meet criteria developed previously to reduce error and bias in scientific overviews.^{26,27} The results are therefore likely to present a valid summary of the literature on the use of CSFD in the prevention of spinal cord deficits in high-risk patients presenting for surgery of the descending thoracic and thoracoabdominal aorta.

Although we originally planned to perform a meta-analysis of the published data on this issue, the lack of randomized controlled trials in this research area led to our decision to present a qualitative overview.

The strength of evidence from an overview depends principally on the quality of the primary studies.²⁸ Stronger inferences can be made from studies designed to minimize the possibility of bias. The most rigorous methodologic design is the randomized controlled trial, followed by (in descending order) the nonrandomized observational study using concurrent controls, the nonrandomized observational study using historical controls, the case series with no controls, and the case report. Studies using historical controls are more intrinsically biased to find an apparent benefit in treatment effect compared with studies using randomized controls.^{29,30} Thus, the primary studies included in this overview are listed in table 2 according to rank order of study design and strength of evidence.

Randomized Controlled Trials

The randomized trial of Crawford *et al.*¹ failed to show a reduction in neurologic insult using CSFD. Although this study was well designed, intraoperative CSFD was limited to 50 ml, which did not decrease CSFP in some patients. Thus, the hypothesis that a reduction in CSFP would improve spinal cord perfusion was not adequately tested. In humans, removal of as much as 500 ml of CSF may be required to reduce CSFP to less than 10 mmHg.²¹ Although there is no evidence from human studies that reducing CSFP *per se* improves spinal cord perfusion, data from animal studies have shown that reducing CSFP by CSFD prevented paraplegia.^{6,7,9,10}

Crawford *et al.*¹ based their sample size on an event rate of 25% in the control group and 5% in the intervention group (CSFD) to give a total sample size of 100 patients. Their study had sufficient power to show an 80% reduction in neurologic deficit with β error = 0.2 and α error = 0.05. Such a dramatic reduction in event rate in the treatment group is unlikely. Using the same

nomogram presented in their article, a sample size of 400 patients would be needed to show a 50% reduction in neurologic deficit assuming an event rate of 20% in the control group and 10% in the intervention group. Changing the expected event rates in the two groups causes the sample size requirements to change dramatically. A 50% treatment effect would still be clinically important, as would a 25% treatment effect. However, the smaller the expected treatment effect, the larger the sample size needed to demonstrate statistical significance. It is interesting to note that the sample size in this study was not achieved by many of the other studies discussed in this overview, which brings into question the validity of results from all studies.

Svensson *et al.*¹⁵ concluded from their randomized trial that the combination of CSFD and intrathecal papaverine reduced the risk of neurologic injury after high-risk thoracoabdominal surgery. This study was terminated early after one third ($n = 33$) of the estimated sample size ($n = 100$) was entered because of a statistically significant difference in the rate of postoperative neurologic deficit ($P = 0.039$). To consider early termination of a trial, one must have sufficiently strong evidence of a treatment effect. The magnitude of the difference must be considered, as well as the level of statistical significance.^{31,32} Significance tests are a useful stopping criterion; however, the main problem with significance testing in interim analysis is that the more frequently one analyzes accumulating data, the greater the chance of finding an effect of treatment (type I error). For a sequence of interim analysis set *a priori*, as in the trial of Svensson *et al.*,¹⁵ a more stringent significance level than $P < 0.05$ must be set (*i.e.*, $P < 0.01$) so that the overall (cumulative) significance level is kept reasonable ($P < 0.05$).³¹ Their P value of 0.039 would not be considered statistically significant for an interim analysis of a clinical trial, and it is unfortunate that the trial was terminated early based on this result. It is probable that their conclusion is biased based on a type I error, and furthermore, the relative therapeutic effects of CSFD *versus* papaverine remains unresolved.

Nonrandomized Trials

Major methodologic limitations that threaten validity were identified in the observational cohort and historical control studies. Variability in the treatment and control populations, intervention, and distribution of confounders (*i.e.*, surgical technique) possibly affected the outcome.¹⁶⁻²² Furthermore, bias in the trial designs may exaggerate the treatment effect. Detail on the evaluation of neurologic outcome was not provided in any study, and all studies except two were retrospective.^{16,18} Some studies included patients with TAs, but we were unable to separate the data between these patients and the high-risk TAAA patients; thus, these data are included in table 2.

The three nonrandomized observational cohort studies¹⁶⁻¹⁸ provided inconclusive data on the potential benefits of CSFD. In all studies, CSFD was used as an adjunct to other modalities being tested for their benefits in spinal cord protection. It is difficult to conclude the relative benefits of each of the therapies given the confounding nature of the intervention itself, the small sample sizes, and the weakness inherent in the nonrandomized observational design employed in these trials. It is important to note that in the trial by Svensson *et al.*,¹⁶ a sample size of 11 in the intervention group and 19 in the control group would not have sufficient power to detect a difference in the rate of neurologic complications. Acher *et al.*¹⁷ grouped three different control treatments together, which is inappropriate and reduces the statistical power of the study. This is a major methodologic flaw which, combined with the fact that naloxone-treated patients received a high-dose opioid anesthetic, makes the study design questionable and may invalidate the authors' conclusion.

Acher *et al.*¹⁷ used their previous results to estimate neurologic deficit for their most recent study¹⁸ in which extensive mathematical modeling was used to examine 80 risk factors for outcome after TAAA surgery. Multiple hypothesis testing jeopardizes the validity of significance tests.³¹ Each test, by definition, has a 5% chance of producing $P < 0.05$, even if the treatments are equivalent. Therefore, when multiple tests are performed, each allowing for a 5% chance of error, the cumulative error can exceed 5%. Hence, investigators typically demand a more stringent level of significance (*e.g.*, 5% divided by the number of comparisons) for each comparison. Excessive use of significance tests produces a certain number of false-positive findings. It is also interesting that this study occurred over a 12-yr period, during which time intensive care, anesthesia, and surgical protocols changed. This analytical type of study may be useful for hypothesis generating.

The four nonrandomized historical control studies used consecutive patients with complete follow-up and pressure-limited CSFD.¹⁹⁻²² Confounders were unequally distributed between the treatment and control groups and may have influenced outcome. It is not stated whether outcome assessment was blinded. In three studies, the intervention group was studied more recently than the control group.¹⁹⁻²¹

Three of the studies advocate use of CSFD.¹⁹⁻²² Murray *et al.*²⁰ did not demonstrate improved neurologic outcome using pressure-limited CSFD. This may reflect the study's lack of power to find a true difference, if in fact any exists. Alternatively, the results could be interpreted differently because there were more type II TAAAs in the intervention group. CSFD may have lowered the incidence of paraplegia in the intervention group to make it equal with the rate in the control group.

The case series category of study design has the great-

est potential for bias and provides the weakest evidence for inferences to be drawn.^{4,8,24,25}

Statistically combining numerical data from these non-randomized studies in a meta-analysis is not appropriate not only because of study design differences but also because the proportion of high-risk patients differ, surgical and anesthetic technique vary among studies, and some studies combined CSFD with other potential modalities for spinal cord protection. Although some studies provided evidence favoring CSFD, these data are unreliable because biases in these study designs probably overestimate the potential therapeutic benefit of CSFD.^{28,29}

Potential Morbidity Associated with Cerebrospinal Fluid Drainage

There has been no morbidity reported with the use of intrathecal catheters in reports of CSFD. Intraoperative heparin has been used in doses adequate for bypass in patients with CSFD catheters with no adverse sequelae.^{20,24} There are no reports of conal herniation with removal of large volumes (500–698 ml) of CSF.^{4,20,21} Although some continue to use CSFD because the reported risk is low, the benefit, if any, is unsubstantiated.

Conclusions and Future Directions

Thoracoabdominal aneurysm repair continues to remain a challenging undertaking for the patient, surgeon, and anesthetist. Although many factors predispose patients to development of paraplegia after TAAA surgery, spinal cord ischemia is clearly the principal factor. No intervention has yet been proven to reduce the incidence of neurologic deficits after TAAA repair. The hypothesis that reducing CSFP will prevent postoperative neurologic deficit after high-risk TAAA surgery has yet to be investigated adequately in humans. In addition, the critical CSFP and duration of CSFD remain to be determined. One animal study suggested that 10 mmHg might be a better endpoint than 15 mmHg.⁹ The role of CSFD for prevention of delayed-onset deficits caused by late spinal cord edema postoperatively also remains undetermined.

The studies presented illustrate the great difficulty in establishing the effects of CSFD on spinal cord protection. Only two trials were performed using a randomized design. The studies that used concurrent or historical control groups had many potential sources of systematic and random error and provided weaker evidence from which to make inferences.^{29,30}

Spinal cord ischemia remains unpredictable and a major cause of morbidity after TAAA repair. Until definitive techniques are developed and evaluated rigorously, centers continue to use different multimodal strategies for whatever benefit they may incur. We suggest that a consensus conference involving surgeons, anesthesiologists, and neurologists should be convened to devise and

test a protocol for spinal cord protection in TAAA surgery. The intervention must be prospectively evaluated in a large randomized multicenter trial with adequate power and blinded outcome to obtain an unbiased answer on which to establish practice guidelines.

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